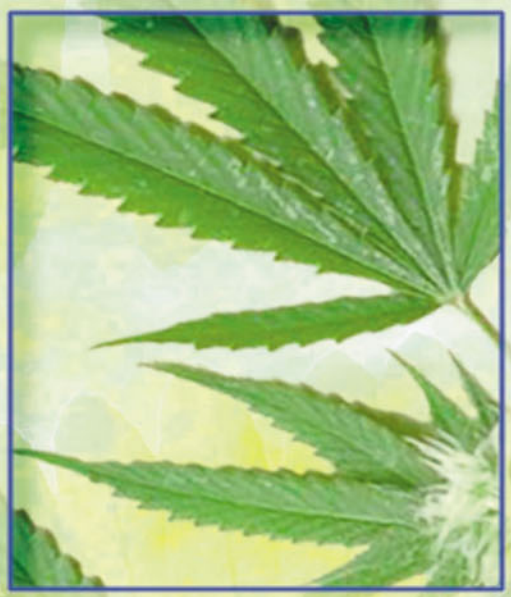
Cannabis and Cannabinoids



Pharmacology, Toxicology, and Therapeutic Potential

Franjo Grotenhermen, MD
Ethan Russo, MD · Editors

Cannabis and Cannabinoids

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THE HAWORTH INTEGRATIVE HEALING PRESS

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Dr. Russo has published numerous peer-reviewed articles on ethnobotany, herbal medicine, and cannabis, and he has lectured nationally on those subjects. He is also the author of a novel, *The Last Sorcerer: Echoes of the Rainforest* (Haworth, 2001). He is the founding editor of *Journal of Cannabis Therapeutics: Studies in Endogenous, Herbal, and Synthetic Cannabinoids.*

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Foreword

There has been renewed interest in the potential medical uses of cannabis (*Cannabis sativa* L.) in recent years, with voters in several states of the United States strongly supporting such a move. Opinion polls suggest similarly strong popular support for the reintroduction of medical cannabis in many European countries. Expert reviews of the medical and scientific evidence on this topic carried out on both sides of the Atlantic in the past few years have concluded that there is a strong case to be made and have encouraged further clinical and scientific research.[1-3] This book is, therefore, very timely. It gives an authoritative and comprehensive review of all the scientific and medical facts, ranging from the botany of the cannabis plant and the complex chemistry of the cannabinoids that it contains, to the potential risks and side effects.

Cannabis-based medicines have been used for thousands of years in Asia, and were popular for 100 years in Western medicine after their introduction in the mid-nineteenth century. They fell out of use largely because of the difficulties that physicians encountered in obtaining consistent results from batches of plant material of varying potency. Patients consequently suffered from either treatment with an ineffective dose or the unwanted intoxicating effects of an overdose that could last for many hours. Modern techniques of plant breeding and cultivation have undoubtedly solved the problem of quality control in the use of herbal cannabis as a medicine, but the issue of a narrow therapeutic window between the desired benefits and the usually unwanted psychic effects remains a challenge.

Many scientists would argue that modern medicines should be single chemical entities wherever possible, rather than complex mixtures of plant constituents. Proponents of herbal cannabis assert that the plant material has advantages over the pure cannabinoid Δ^9-THC (delta-9 tetrahydrocannabinol)—but this argument is confused by the fact that herbal cannabis is usually smoked whereas THC is taken orally. The oral route for THC is notoriously slow and unreliable, whereas smoking is a very efficient way of delivering the drug quickly and in a manner that allows flexible dosetitration. Smoking, however, carries medical risks. In the short term, the irritant effects of cannabis smoke can lead to bronchitis; in the long term, a far more serious hazard is the potential for increased risk of cancers of the lung, airways, and mouth. Although the cancer risk cannot be accurately quantified as yet, in my view it is one of the most serious potential dangers that need to be considered. Better methods for delivering both herbal

cannabis and pure THC are urgently needed. Although there have been suggestions that cannabis has adverse long-term effects on pregnancy, the immune system, fertility, and cognition, the preponderance of available evidence suggests that these are far less severe than originally thought.

The 1990s witnessed major advances in our scientific understanding of how THC and other cannabinoids act on the central nervous system. The discovery that the brain and some other organs contain specific protein receptors that recognize the drug and trigger cell responses is analogous to the discovery in the early 1970s of opiate receptors in the brain that bind morphine and other opiates. As with the opiates, the discovery of specific cannabinoid receptors prompted the search for putative naturally occurring chemicals that interact with the receptors. This led to the discovery of anandamide as the first of the naturally occurring endogenous cannabinoids. Although anandamide belongs to an entirely different chemical class than THC, it is bound by the same receptors. These discoveries shed entirely new light on the pharmacology of cannabis. From the original goal of studying a psychotropic plant cannabinoid, we now see instead the opportunity of revealing a wholly novel physiological control system in the body. Exploration of synthetic anandamide-like chemicals may be one way to obtain improved cannabinoid-based medicines. The pace of discovery has been so rapid in recent years that it would also not be unreasonable to anticipate that more members of the cannabinoid receptor family and additional endogenous cannabinoid substances may yet be discovered in the future. This, in turn, could lead to new therapeutic opportunities, perhaps involving a number of natural cannabinoids that do not bind known cannabinoid receptors but nevertheless have some important pharmacological effects.

These and many other topics are admirably dealt with in this book. The editors should be congratulated for having assembled such a well-balanced volume, written by experts in their fields. This book should provide a valuable information resource to those interested in this field and should help to inform the debate on these topics.

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REFERENCES

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2. Joy JE, Watson SJ, Benson JA, Eds. *Marijuana and medicine: Assessing the science base*. Institute of Medicine. Washington, DC: National Academy Press, 1999.

3. House of Lords Select Committee on Science and Technology. *Cannabis: The scientific and medical evidence*. London: The Stationery Office, 1998.

Preface

> I wish to propose for the reader's favourable consideration a doctrine which may, I fear, appear wildly paradoxical and subversive. The doctrine in question is this: that it is undesirable to believe a proposition when there is no ground whatever for supposing it true.
>
> Bertrand Russell
> From "Introduction:
> On the Value of Scepticism"
> *Sceptical Essays,* 1928

Cannabis is still sending *"signals of misunderstanding."*[1-3] The result is an exaggeration of beneficial or deleterious effects as well as occasional intermixture of medical science with other moral categories.

This book deals with health aspects of the cannabis plant and the cannabinoids while mainly factoring out societal aspects. Some authors refer to social topics that require discussion even within the bounds of a narrow handling of medicinal aspects.

Scientists with different views on the therapeutic benefits of cannabis and with different assessments of potential harms get a hearing, so that the book reflects and considers the frictions and controversies surrounding many themes in this area.

The different opinions and judgments, often only reading between the lines, possibly result in a deeper insight into the controversial aspects of this topic than a more homogenous book might allow. At the same time, it was the intention of the editors to offer a clearly structured overview of the subject, as well as an insight into many facets of modern cannabinoid research. Leading experts in their fields have contributed to this volume. Most are members of the International Cannabinoid Research Society, which includes about 200 scientists. Some of them are also members of the International Association for Cannabis as Medicine, which deals particularly with the medical use of cannabis and the cannabinoids.

We would like to cordially thank all authors for their pleasant cooperation in contributing their texts to the project. We were particularly glad to have their many proposals for additional topics and suggested modifications. These completed and significantly improved the manuscript from concept to final realization. For their assistance in translation work and in

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Franjo Grotenhermen
Ethan Russo

REFERENCES

1. Nahas GG, Greenwood A. The first report of the National Commission on Marihuana (1972): Signal of misunderstanding or exercise in ambiguity. *Bulletin of the New York Academy of Medicine* 1974;50(1):55-75.

2. National Commission on Marihuana and Drug Abuse. *Marihuana: A signal of misunderstanding. First report.* Washington, DC: U.S. Government Printing Office, 1972.

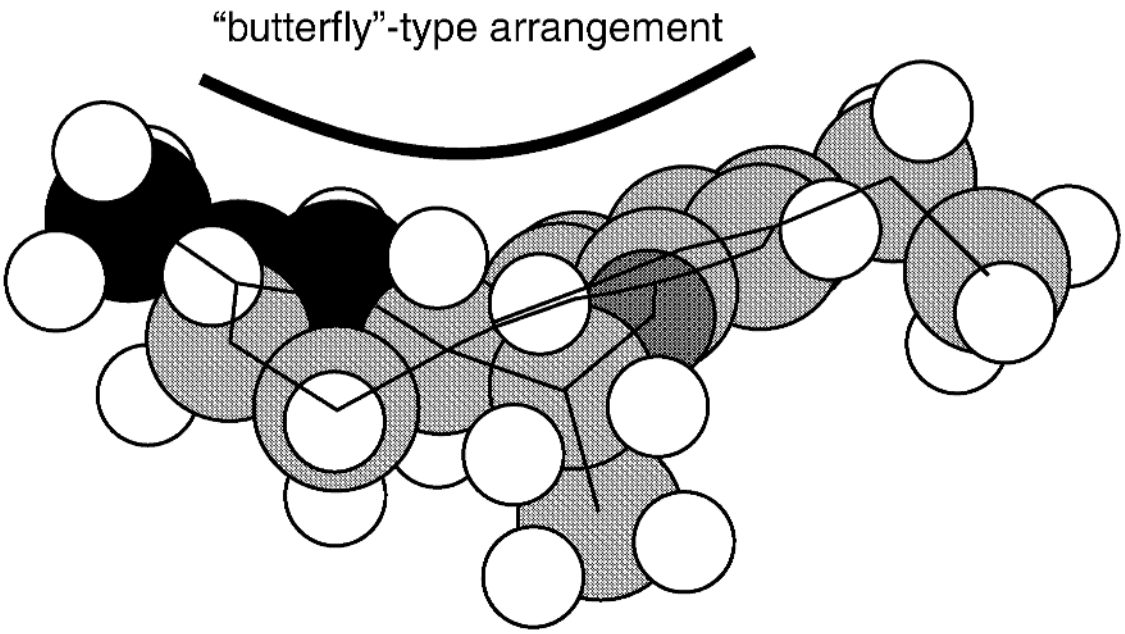
3. Ungerleider JT. Marijuana: Still a "signal of misunderstanding." *Proceedings of the Association of American Physicians* 1999;111(2):173-181.

Definitions and Explanations

THC, Δ^9-THC (delta-9-THC)

THC (tetrahydrocannabinol) (see Figure 1) usually refers to the naturally existing isomer of Δ^9-THC, but also may include Δ^8-THC (see Chapter 3). Delta-9-tetrahydrocannabinol and Δ^1-tetrahydrocannabinol (Δ^9-THC, Δ^1-THC) are two names for the same molecule according to different numbering systems (monoterpenoid and dibenzopyran nomenclature) (see Chapter 2). Generally the natural (-)-*trans*-isomer of Δ^9-THC of the cannabis plant, the (-)-Δ^9-*trans*-tetrahydrocannabinol or dronabinol is designated. Chemically, Δ^9-THC is defined as (6aR-trans)-6a,7,8,10a-tetrahydro6,6,9-trimethyl-3-

FIGURE 1. Three-Dimensional Model of Δ^9-THC (Dronabinol)



Source: Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and Medicine*. Totowa, NJ: Humana Press, 1999, p. 82. Reprinted with permission.

TABLE 1. Chemotypes of Cannabis

Chemotype	Products	Leading cannabinoids	THC content	Psychoactivity
Drug type	marijuana, hashish	Δ^9-THC	1-20%	yes
Intermediate type		Δ^9-THC, CBD	0.3-1.0%	possible
Fiber type	fiber, edible oil	CBD (cannabidol)	<0.3%	no

pentyl-6H-dibenzo[b,d]pyran-1-ol with the chemical short formula $C_{21}H_{30}O_2$ and a molecular weight of 314,47 kDa.

Dronabinol, Marinol

Dronabinol is another name for the synthetically manufactured (-)-*trans*-isomer of Δ^9-THC, often used in a medical context in the scientific literature. Marinol is a dronabinol preparation, dissolved in sesame oil, as capsules of 2.5, 5, and 10 mg dronabinol. It is a registered trademark of Unimed Pharmaceuticals, Inc. Marinol is available in the United States, Canada, and some European countries.

Nabilone

Nabilone is a synthetic derivative of Δ^9-THC with a slightly modified molecular structure (see Chapter 2). With regard to pharmacological activity, 1 mg nabilone corresponds to about 10 mg of dronabinol. It is a registered trademark of Eli Lilly and Co. and marketed under the name Cesamet. It is on the market in the United Kingdom and Canada, and in some other European countries.

Cannabinoids

The term "cannabinoid" has different meanings. In a more narrow sense, it designates the natural phytocannabinoids of the hemp plant. In the broadest sense, it includes all ligands of the cannabinoid receptors and related compounds (see Chapter 2). The endogenous ligands of the cannabinoid receptors, belonging to distinct chemical classes as compared to the phytocannabinoids, have been termed endocannabinoids.

TABLE 2. Chronological Table 1

- 1937-1940: Identification of first cannabinoids[7]
- 1941: Synthesis of the first synthetic cannabinoid, Synhexyl[1]
- 1964: Revelation of the exact chemical structure of Δ^9-THC[3]
- 1988: Evidence of cannabinoid receptors in the CNS
- 1990: Cloning of the CB_1-receptor (cannabinoid-1-receptor)[10]
- 1992: Discovery of the first endocannabinoid anandamide (N-arachidonylethanolamide, AEA)
- 1993: Cloning of the CB_2-receptor (cannabinoid-1-receptor)[10]
- 1994: Development of SR 141716A, the first antagonist at the CB_1-receptor[10]
- 1995: Discovery of 2-arachidonoylglycerol (2-AG), another endogenous ligand at the CB receptor

Cannabis, *Hemp, Marijuana, Hashish*

Cannabis sativa L. is the botanical name and Latin binomial of hemp. Marijuana (marihuana) is a colloquial name for dried leaves and flowers of cannabis varieties rich in THC (1 to 20 percent Δ^9-THC). The median content of THC of confiscated marijuana in the United States in 1997 was 4.2 percent. Hashish is an Arabic name for cannabis resin or compressed resin glands, containing 5 to 20 percent Δ^9-THC. Depending on THC and cannabidol (CBD) content, "hemp" can be divided into fiber and drug types. There are regional differences in the employment of the terms cannabis, hemp, and marijuana. In the United States and Canada the term "hemp" is usually only applied to fiber hemp in contrast to the term "marijuana," while in many regions of Europe hemp ("Hanf") can be applied to drug types as well (in the sense of the old term "Indian hemp"). In the United Kingdom the term cannabis is preferred in the context of medical use; in the United States and Canada the term marijuana ("medical marijuana") is used most often.

TABLE 3. Chronological Table 2

- February 19-20, 1997: "Workshop on the Medical Utility of Marijuana" of the NIH (National Institutes of Health, USA).[9]
- November 18, 1997: The British Medical Association publishes the book *Therapeutic uses of cannabis* and asks the courts to use compassion in dealing with cases involving seriously ill people who possessed cannabis.[2]
- May 20-21, 1998: "International Conference on Marijuana and Medicine" of the International Cannabinoid Research Society in New York.[8]
- November 11, 1998: The British House of Lords presents their report on cannabis and demands legal avenues to use cannabis therapeutically.[5]
- December 2-5, 1998: Conferences on the medical use of cannabis in Cologne and Frankfurt (Germany), "Frankfurt Resolution" in support of the medical use of marijuana.[4]
- March 17, 1999: Publication of "Marijuana and medicine: Assessing the science base" of the Institute of Medicine (USA), result of a two year investigation on behalf of the ONDCP commissioner of the federal government on the occasion of the successful Californian voters initiative Proposition 215.[6]
- 1999/2000: Approval/start of several clinical studies with natural cannabis products in Germany, Switzerland, the UK, and Canada.

REFERENCES

1. Adams R, Loewe S, Jelinek C, Wolff H. Tetrahydrocannabinol homologs with marihuana activity. IX. *Journal of the American Chemical Society* 1941;63:1971-1976.

2. British Medical Association. *Therapeutic uses of cannabis*. Amsterdam: Harwood Academic Publishers, 1997.

3. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society* 1964;86:1646-1647.

4. Grotenhermen F, Saller R, eds. Cannabis und Cannabinoide in der Medizin. *Forschende Komplementärmedizin [Research in Complementary Medicine]* 1999; 6(Suppl 3).

5. House of Lords Select Committee on Science and Technology. *Cannabis. The scientific and medical evidence*. London: The Stationery Office, 1998.

6. Joy JE, Watson SJ, Benson JA, eds. *Marijuana and medicine: Assessing the science base*. Washington, DC: Institute of Medicine, National Academy Press, 1999.

7. Loewe S: Cannabiswirkstoffe und Pharmakologie der Cannabinole. *Archiv für Experimentelle Pathologie und Pharmakologie* 1950;211(2):175-193.

8. Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999.

9. NIH-Workshopprotokoll 1997: <www.nih.gov/news/medmarijuana/MedicalMarijuana.htm>.

10. Pertwee RG. Pharmacology of cannabinoid CB_1 and CB_2 receptors. *Pharmacology and Therapeutics* 1997;74(2):129-180.

PART I: BOTANY, TAXONOMY, CHEMISTRY, AND HISTORY

Chapter 1

Botany of Natural *Cannabis* Medicines

Robert C. Clarke
David Paul Watson

INTRODUCTION

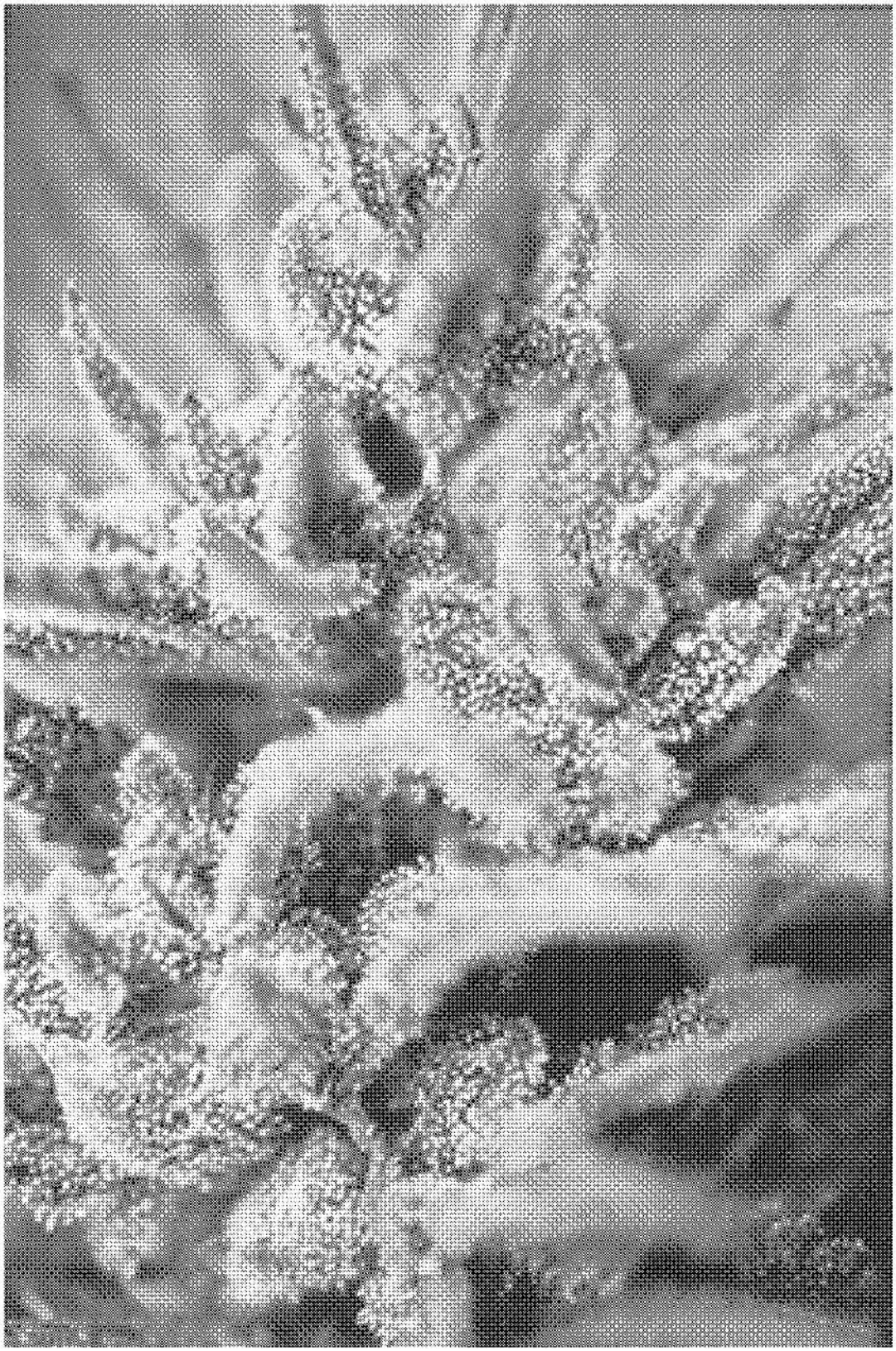
Cannabis is among the very oldest of economic plants, providing fiber, edible seed, and drug resin. Human selection for varying uses and natural selection pressures imposed by diverse climates have resulted in a wide variety of growth forms and chemical compositions. Innovative classical breeding techniques have been used to improve drug cannabis, resulting in many cannabinoid-rich cultivars suitable for medical use. The production of cannabinoids is unique to *Cannabis,* and cultivars with specific chemical profiles are being developed for diverse potential pharmaceutical uses.

NATURAL LIFE CYCLE

Cannabis is an annual plant, propagated from seed, and grows vigorously in open sunny environments with light, well-drained soil and ample nutrients and water, and reaches up to five meters (16 feet) in height in a four- to six-month growing season. Feral *Cannabis* populations are frequently found in association with human habitation. Agricultural lands, roadsides, exposed riverbanks, meadows, and disturbed lands are ideal habitats for wild and feral *Cannabis,* as they provide adequate sunlight.

Seeds usually germinate in three to seven days. During the first two to three months of growth juvenile plants respond to increasing day length with more vigorous vegetative growth characterized by an increasing number of leaflets on each leaf. Later in the season (after the summer solstice), shorter days (actually longer nights) induce flowering and complete the life cycle (see Figure 1.1). Cannabis begins to flower when exposed to short day

FIGURE 1.1. Close-Up Photo of a *Cannabis* Inflorescence, with Each Seed Concealed Within a Perigonal Bract Covered with Glandular Trichomes



lengths of 12 to 14 hours or less (long nights of 10 to 12 hours or more) depending on its latitude of origin. However, a single evening of interrupted darkness can disrupt flowering and delay maturation. If an individual plant is not crowded by its neighbors, as is the case for the crops intended for seed or drug production, flower-bearing limbs will grow from small buds located at the base of the leaf petioles originating from nodes along the main stalk. The flowering period is characterized by leaves bearing decreasing numbers of leaflets.[1]

Cannabis is normally a dioecious plant, with male and female flowers developing on separate plants. The sexes of *Cannabis* are anatomically indistinguishable before they begin flowering. However, Mandolino and Ranalli[7] report success using RAPD analysis to identify male-specific DNA markers. The development of male and female plants varies greatly. The male flowers hang in loose clusters along a relatively leafless upright branch, in contrast to crowded clusters of individual female flowers at the base of each leaf along the branch. Male *Cannabis* flowers require air currents to carry pollen grains to the female flowers, which results in fertilization and consequent seed formation. The male plants finish shedding pollen and die before the seeds in the female plants ripen four to eight weeks after being fertilized. Pollen has been frozen and successfully used for seed production up to three years later.

The single seed in each female flower ripens in about three to eight weeks and will either be harvested by humans, eaten by birds or rodents, or drop to the ground. A large female plant can produce over one kilogram of seed. This completes the natural four to six month life cycle. If the seeds are not consumed by birds or rodents, they may germinate the following spring. *Cannabis* seeds are a balanced source of essential fatty acids (EFAs), and easily digestible protein and are usable as human food or animal feed (see Chapter 38). EFAs have been shown to have many important physiological roles and hemp seed oil is a valuable nutraceutical.[3]

AGRICULTURAL FIELD PRODUCTION

For hemp crops grown for fiber or seed, both male and female plants are usually left in the field until harvest. The male plants pollinate the females and then die before the seeds ripen. In the early 1970s, a handful of North American marijuana cultivators began to grow *sinsemilla* (Spanish for "without seed") marijuana. The sinsemilla effect is achieved by eliminating staminate plants from the fields, leaving only the unfertilized pistillate plants to mature for later harvest. In lieu of setting seed in the earliest flowers, the pistillate plants continue to produce additional flowers, which are covered by resin glands, thus increasing the percentage of psychoactive and medically valuable Δ^9-tetrahydrocannabinol (THC) or other cannabinoids.

This technique was originally developed in India, but historians are unsure of its history prior to 1800. Since 1975, sinsemilla has been the primary style of North American and European marijuana production.

Throughout the 1980s, the vast majority of domestically produced North American drug cannabis was grown outdoors, but in the 1990s the popularity of growing in greenhouses and indoors under artificial lights rapidly expanded. Crops grown from seed make large plants of both genders that take up a lot of space, and exhibit a range of characteristics. A *Cannabis* breeder relies on this variation as potential to improve varieties. However, a drug cannabis producer wants a profitable and uniform crop, and uses female clones that improve grow room yields, but preclude the possibility of seed production and varietal improvement.

VEGETATIVE CROP PRODUCTION

Much of the *Cannabis* presently used for medical purposes is grown indoors under artificial lights. Metal halide and sodium vapor light systems are most often set up in attics, bedrooms, or basements. Most modern indoor growers produce vegetatively propagated crops. Only female drug *Cannabis* plants are economically valuable, and garden space is limited. It is both difficult and expensive to purchase reliable drug *Cannabis* seed, sales of which are prohibited in many nations. In addition, the legal systems of many nations penalize growers of large quantities of cannabis with harsher penalties. Under artificial growing conditions, crops are reproduced vegetatively by rooting cuttings of only female plants, transplanting and inducing flowering almost immediately. Cuttings taken from one plant are all identical members of a single clone and they will all respond in the same way to environmental inputs. Given that environmental influences are constant, the clone will yield a uniform crop of nearly identical seedless females each time it is grown.

Female "mother" plants are maintained in a constantly vegetative state under 18 hour or longer day lengths. Serial cuttings can be removed, rooted, grown under long day length and used to replace older mother plants, indefinitely. If the cutting material remains free of viruses or other pathogens there is no loss of vigor after multiple rounds of vegetative propagation. Whenever they are required, rooted small cuttings (10 to 30 cm tall) are moved into a flowering room with a day length of 10 to 13 hours, to mature 7 to 14 weeks later.

Cloned plants can mature fully, form flowers from top to bottom and look like a rooted branch from a large plant grown from seed when they are less than one meter tall. The length of time between the induction of flowering under short days and final maturity of the female floral clusters depends largely on the variety being grown and the day length. Some cultivars ma-

ture much more quickly than others. Cannabis plants mature faster when they are given shorter day lengths of 10 hours, but most cultivars have an optimum day length requirement, for maximum production, of around 12 or 13 hours. Under ideal conditions, yields of dried floral clusters can reach 1,200 grams per square meter per year or more, as a result of multiple cropping three or five times per year.

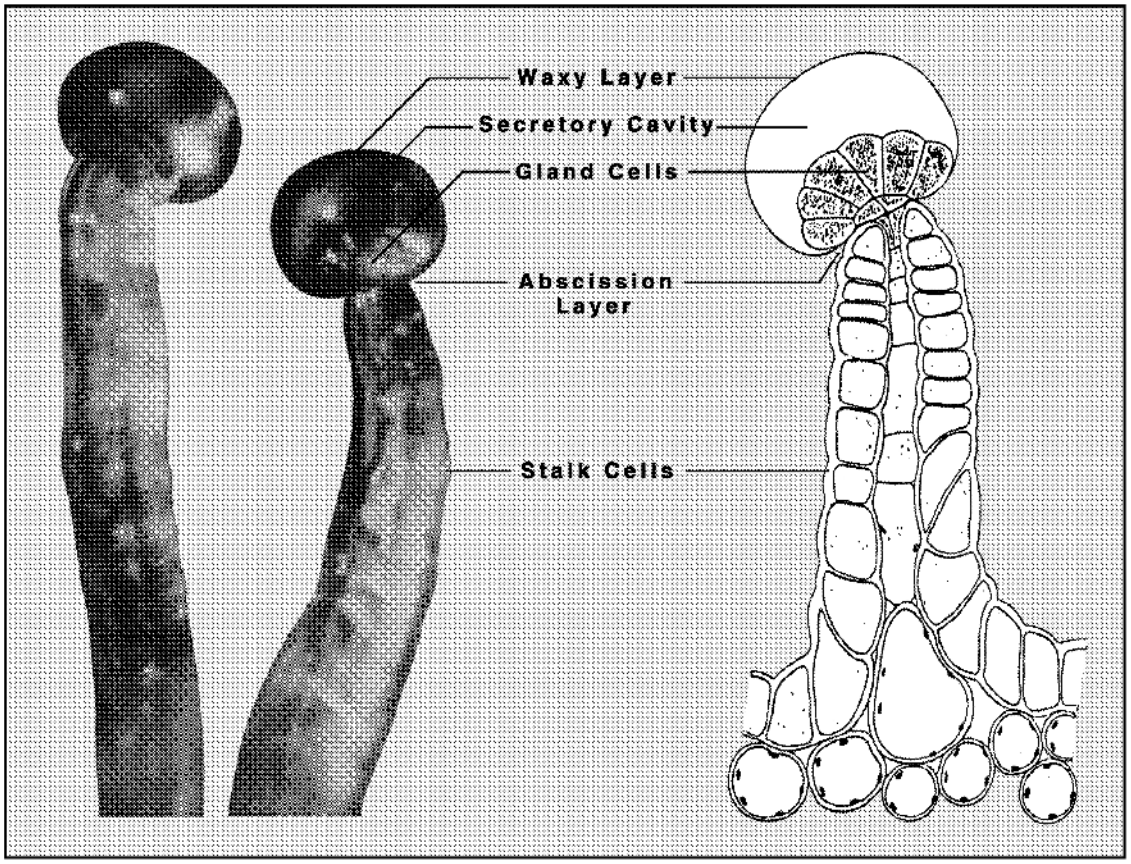
Male plants can also be kept in a vegetative state and induced to flower when pollen is required. However, they are often more difficult to revert from flowering to the vegetative state than females. In vitro techniques would allow long-term storage of wide varieties of living germplasm. Several research groups have reported success[6,7] with reproducing undifferentiated callus tissue and meristems.

RESIN GLAND DEVELOPMENT

When resin gland development commences, the medically important cannabinoids and the associated terpenoids begin to appear (see Figure 1.2). Terpenoids are the primary aromatic principles found in the essential oil of *Cannabis,*[5,10] although cannabinoids are odorless. Most interesting medically, are the cannabinoid-rich terpenoid secretions of the head cells of glandular hairs distributed across the surface of the female inflorescence. (Male plants are usually of no consequence for drug production, as they have few glandular trichomes.) Solitary resin glands most often form at the tips of slender trichome stalks which form as extensions of the plant surface. The cluster of one or two dozen head cells atop each stalk secrete aromatic terpenoid-containing resin with a very high percentage of cannabinoids (≥80 percent) which collect under a thin waxy membrane surrounding the secretory head cells.[2] The secreted resin component is, in large part, segregated from the secretory cells. This isolates the resin from the atmosphere as well as membrane-bound enzyme systems within the secretory cells, possibly protecting the terpenoids and cannabinoids from oxidative degradation and enzymatic change. At the base of each cluster of resin head cells lies an abscission layer allowing the gland and its secreted resin to be easily removed. *Cannabis* resin (hashish or charas) is simply formed from resin glands that have been rubbed or shaken from the plant and compressed into a dense mass.[2]

Resin glands containing cannabinoids and terpenoids may have an adaptive significance for the *Cannabis* plant as defense against environmental challenges, including insect and fungal attack.[9] However, *Cannabis* crops are still subject to infestation by a wide variety of pests, particularly under greenhouse conditions.[8] Certainly, the intoxicating effects of this *Cannabis* resin have increased cannabis predation by humans, as well as encouraged its domestication, thus dramatically widening its distribution.

FIGURE 1.2. Microscope Photograph and Drawing of a Cannabis Resin Gland, with Secretory Head Cells Easily Visible Underneath the Transparent Cannabinoid- and Terpenoid-Rich Resin

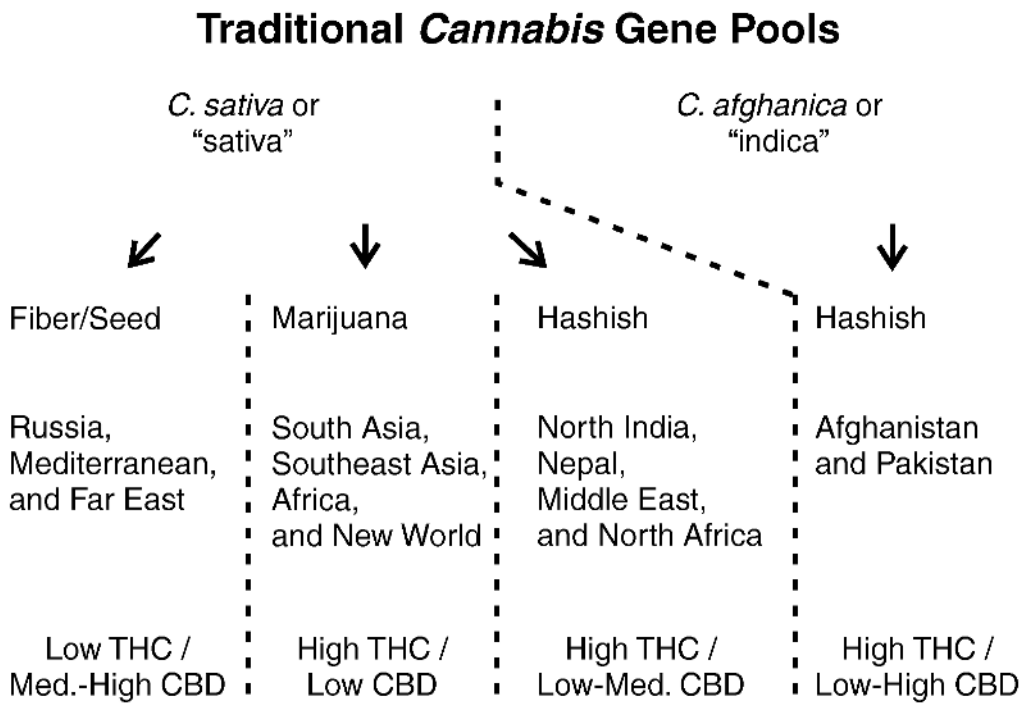


Source: Drawing from RC Clarke. *Hashish!* Los Angeles: Red Eye Press, 1998. Photo courtesy of Joop the Crystal Man.

CANNABIS *ORIGINS*

Cannabis likely originated in Central Asia or near the Altai or the Tian Shan mountains and was first cultivated in China and soon after in India. Different cultures have traditionally used cannabis for a variety of purposes (see Figures 1.3 and 1.4). European and eastern oriental societies most often used cannabis for its strong fibers and nutritious seeds. Races of fiber and seed *Cannabis* are nearly always relatively low in THC, with an approximately twofold cannibidiol (CBD) content averaging about twice as high. THC is the primary psychoactive compound produced by cannabis. Nonpsychoactive CBD is the other most common naturally occurring cannabinoid. African, Middle Eastern, South Asian, and Southeast Asian cultures used cannabis widely for its psychoactive properties and to a lesser extent for fiber and food.

FIGURE 1.3. The Four Major *Cannabis* Gene Pools



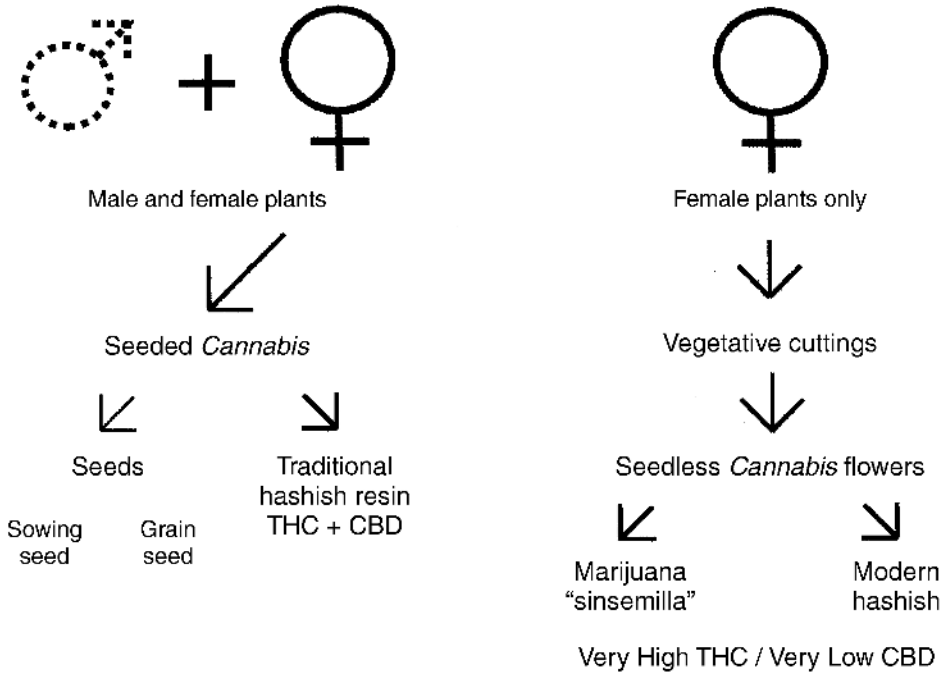
Most modern medical *Cannabis* varieties are a blend of traditional "sativa" marijuana varieties with "indica" hashish varieties.

Source: Adapted from Meijer de EPM. *Cannabis* germplasm resources. In Ranalli P, ed. *Advances in Hemp Research.* Binghamton, NY: The Haworth Press, 1999, pp. 133-151; and from Clarke RC, *Hashish!* Los Angeles: Red Eye Press, 1998.

Note: The traditional *Cannabis* gene pools originate either from *C. sativa,* which comprises the vast majority of naturally occurring hemp and drug land races, or from *C. afghanica* from Afghanistan and Pakistan, which is commonly called "indica" and has become a component in many modern drug *Cannabis* cultivars.

The vast majority of the varieties from these regions are high in psychoactive THC (often 5 to 10 percent) with a widely varying CBD content (usually nil, but often up to 5 percent). The South Asian section of the *Cannabis* gene pool was spread by humans far and wide from Africa to Sumatra by early traders and eventually to the equatorial New World. Cannabis was adopted in many of these locations and improved as a psychoactive drug plant. All modern drug varieties used as medical cannabis are derived from these traditional drug varieties.

FIGURE 1.4. Recreational and Medical *Cannabis* Sources



Note: Both recreational and medical *Cannabis* typically available to users either originate from seeded field-grown plants used primarily for hashish production or seedless plants grown primarily for "sinsemilla" and occasionally for modern "high-tech" hashish.

CANNABIS *TAXONOMY*

Modern taxonomists have variously characterized *Cannabis*. All taxonomists recognize the species *Cannabis sativa*. Small and Cronquist[13] subdivide *C. sativa* into two subspecies each with two varieties. Schultes et al.[11] divide *Cannabis* into three species; *C. sativa, C. indica,* and *C. ruderalis*. Several other researchers do not preserve *C. ruderalis,* but recognize both *C. sativa* and *C. indica*.[12,14,15] The present authors consider *C. sativa* to circumscribe all wild, hemp, and drug *Cannabis* races with the possible exception of the races used for hashish production in Afghanistan and Pakistan. These morphologically and chemically distinct races may deserve the separate specific name of *C. afghanica* following the variety name for *C. indica* determined by Vavilov.[14] Validation of this theory awaits further chemotaxonomic and genetic research.

In all of these systems, *C. sativa* represents the largest and most diverse taxon. *C. afghanica* is commonly referred to by marijuana breeders and

growers, as well as medical cannabis users, as "indica." Chemovars of this variety have their own distinctive acrid organic aromas and are often rich in CBD as well as THC. The great variety of chemical, physiological, and morphological traits encountered in *Cannabis* has proven very attractive to plant breeders for years.

MEDICAL CANNABIS *TODAY*

Drug *Cannabis* available to the medical user can be assigned to one of two categories. Marijuana (domestically produced and imported cannabis flowers) is nearly always grown from high-THC varieties (up to 20 to 25 percent dry weight in trimmed female flowers) containing very little CBD. Hashish or charas (compressed cannabis resin) is made from varieties that are predominantly THC (up to 10 percent), but they often contain up to 5 percent CBD. Clean high-THC profiles result from marijuana growers making seed selections from individual favorable plants with high THC levels. Hashish is produced by bulk processing large numbers of plants, and, therefore, growers are unable to make seed selections from individual particularly potent plants so the CBD level tends to remain at more natural limits. Hashish cultivars are bred for resin quantity rather than potency, so the farmer selects plants and saves seeds by observing which ones produce the most resin, rather than if it contains THC or CBD. Afghan populations contain approximately 25 percent plants that are rich in CBD with little THC, 50 percent that contain both CBD and THC, and 25 percent that contain little CBD and are rich in THC. CBD is suspected of having effects on the primary psychoactive compound THC and in a medical setting it may also have useful modulating effects on THC or valuable effects of its own. However, analytical surveys of 80 *Cannabis* varieties in the Netherlands (D.W. Pate, personal communication, 1999) and 47 samples in California[4] show that nearly every sample contained predominantly THC usually with less than 5 percent of the other combined cannabinoids. Higher levels of THC and other medically effective cannabinoids and terpenoids are healthier for patients using smoked cannabis as they can smoke less to achieve the same dosage and effect.

MEDICAL CANNABIS *TOMORROW*

Cannabis breeders are continually searching for new sources of exotic germplasm and will develop new varieties that prove particularly effective as medicines. Pure "indica" varieties are still highly prized breeding stock and new "indica" introductions from Central Asia are occasionally re-

ceived. *C. sativa* varieties from South Africa have recently gained favor with breeders, as they mature early.

HortaPharm BV in the Netherlands has an ongoing breeding project to develop high-yielding *Cannabis* cultivars of known cannabinoid profile. The aim of the project is to create varieties that produce only a single one of the four major cannabinoid compounds (e.g., THC, CBD, CBC, CBG, or their propyl homologues) as well as selected varieties with predictable mixed cannabinoid profiles. Some of these single cannabinoid varieties are being commercially exploited by GW Pharmaceuticals Ltd. in England, which began clinical trials in 1999 with whole cannabis extracts.

CONCLUSION

Largely as a response to political pressure and the limited availability of high quality commercial cannabis, the home growing of this crop, whether for medical or recreational use, is a trend rapidly spreading across North America and Europe. Cannabis smoking and cultivation for personal medical use will eventually be legalized or tolerated in many places, if not by the public openly favoring marijuana legalization, then by increasing awareness of the advantages of this potentially useful medicine.

REFERENCES

1. Clarke RC. *Marijuana Botany.* Berkeley: Ronin Publishing, 1981.

2. Clarke RC. *Hashish!* Los Angeles: Red Eye Press, 1998.

3. Pate DW. Hemp seed: A valuable food source. In Ranalli P, ed. *Advances in Hemp Research.* Binghamton, NY: The Haworth Press, 1999, pp. 243-255.

4. Gierienger D. Medical *Cannabis* potency testing. *Bulletin of the Multidisciplinary Association for Psychedelic Studies* 1999;9(3):20-22.

5. Hendriks H, Malingre TM, Batterman S, Bos R. The essential oil of *Cannabis sativa* L. *Pharmaceutisch Weekblad* 1978;133:413-424.

6. Liu Y, Tang X. Green seedling of hemp acquired by tissue culture. *China's Fibre Crops* 1984;2:19, 29 (in Chinese).

7. Mandolino G, Ranalli P. Advances in biotechnological approaches for hemp breeding and industry. In Ranalli P, ed. *Advances in Hemp Research.* Binghamton, NY: The Haworth Press, 1999, pp. 185-212.

8. McPartland J, Clarke RC, Watson DP. *Hemp Diseases and Pests.* Wallingford, UK: CAB International, 2000.

9. Pate DW. The phytochemistry of *Cannabis:* Its ecological and evolutionary implications. In Ranalli P, ed., *Advances in Hemp Research.* Binghamton, NY: The Haworth Press, 1999, pp. 1-19.

10. Ross RA, ElSohly MA. The volatile oil composition of fresh and air-dried buds of *Cannabis sativa*. *Journal of Natural Products* 1996;59:49-51.

11. Schultes RE, Klein WM, Plowman T, Lockwood TE. Cannabis: An example of taxonomic neglect. *Botanical Museum Leaflets, Harvard University* 1974;23(9):337-364.

12. Serebriakova TI. Fiber plants. In Wulff EV, ed. *Flora of Cultivated Plants*. Volume 4, Part 1. Moscow and Leningrad: State Printing Office, 1940 (in Russian).

13. Small E, Cronquist A. A practical and natural taxonomy for Cannabis. *Taxon* 1976;25(4):405-435.

14. Vavilov N, Bukinich DD. *The Bulletin of Applied Botany, of Genetics, and Plant Breeding,* Agricultural Afghanistan 1929;33(Suppl):378S-382S, 474S, 480S, 584S-585S, 604S.

15. Zhukovskii PM. Cultivated plants and their wild relatives. In Hudson PS, ed. London: Commonwealth Agricultural Bureau, 1950.

Chapter 2

Taxonomy of Cannabinoids

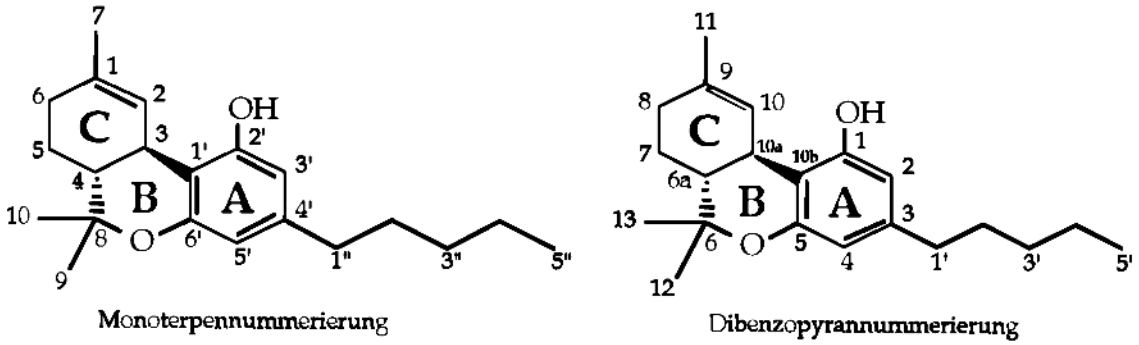
David W. Pate

Cannabinoids were originally regarded as any of a class of "typical C_{21} groups of compounds present in *Cannabis sativa* L."[24] From this rather restricted pharmacognostic definition, considerable expansion is now required. The modern definition is better termed with more emphasis on synthetic chemistry and on pharmacology, and should also encompass kindred structures, or any other compound that affects cannabinoid receptors. However, this has created several chemical subcategories that, for the purposes of this study, take into consideration the various forms of natural and synthetic compounds. The natural compounds are conveniently divided into plant versus animal compounds, and synthetic variations on the former compounds may be placed into categories that reflect their degree of kinship ("classical" versus "nonclassical") with the phytocannabinoids. Of course, synthetic anandamide-type compounds also occur, and these are herein separated from the corresponding "endocannabinoids," as "synthetic analogues" and "amidase inhibitors." The last category includes both aliphatic and aromatic compounds, most of which do not fit into cannabinoid receptors, but all of which indirectly promote anandamide accumulation in situ.

PHYTOCANNABINOIDS

Exploration of cannabinoids began with the methodical dissection of natural products contained within the botanical source. The resulting extensive catalog of discovery has been amply reviewed elsewhere (see Chapter 3), and will only be briefly summarized here. These unique compounds, which include the major active drug constituents of this genus, have been numbered according to two major systems of nomenclature (see Figure 2.1): the monoterpenoid system originally employed in Europe, and the dibenzopyran

FIGURE 2.1. Cannabinoid Numbering Systems



system more commonly used today in North America. The latter system will be employed here. The function of these compounds in the plant is unknown, but they possibly counter various ecological challenges.[22]

Variable amounts of Δ^9-tetrahydrocannabinol (THC) are accompanied by significant quantities of cannabigerol (CBG), cannabidiol (CBD), and cannabichromene (CBC). Cannabinoids were originally thought to exist in the plant as phenolic compounds, but later research demonstrated them to also possess a carboxylic acid moiety, which decarboxylates readily over time, upon heating or under alkaline conditions. There are over 60 cannabinoids present in the plant (see Chapter 3), although most of these, plus hundreds of other compounds, exist only in small to minuscule quantities, relative to the four major cannabinoids and their sporadically occurring propyl, and rare methyl, C-3 homologues.

SYNTHETIC ANALOGUES

Classical

Research into the actions of these natural compounds, and particularly THC, has led to the creation of many artificial variations on their basic molecular structures, the chemistry and pharmacology of which has been extensively reviewed (e.g., by Razdan[24]). In this context, "classical" synthetic cannabinoids will be considered as those that retain the natural cannabinoid ring structures and their oxygen atoms.

Synhexyl was the first synthetic cannabinoid drug (e.g., see review by Adams and colleagues[2]). It has approximately 30 percent of the potency of the natural product[17] and closely resembles THC, except that its double bond resides at the 6a,10a position and the natural C-3 pentyl chain is lengthened by one methylene.

One of the first modifications of natural THC involved altering the position of its double bond. Refluxing CBD or Δ^9-THC[12] in acidic conditions

yields Δ^8-THC, a less labile compound possessing approximately 65 percent of the natural isomer potency.[16]

Variations at C-11 provide additional modifications of potency. As with the metabolic conversion of Δ^9-THC, synthetic oxidation of Δ^8-THC to the alcohol (e.g., see review by Ben Zvi and colleagues[6]) increases psychoactivity.[15] For either isomer, additional "C" ring hydroxylation, or further oxidation at C-11 to the carboxylic acid eliminates this action, and also occurs metabolically (see Chapter 6). Interestingly, THC carboxylic acid derivatives may prove useful as anti-inflammatory analgesics (see Chapter 35).

Nabilone (see Figure 2.2) is a keto-cannabinoid[3,33] and the only classical synthetic THC analogue that can be prescribed, being available in Canada, Switzerland, and the United Kingdom as Cesamet. Lethal toxicity upon chronic administration has been found in the dog model, although its relevance to human use is uncertain.[19]

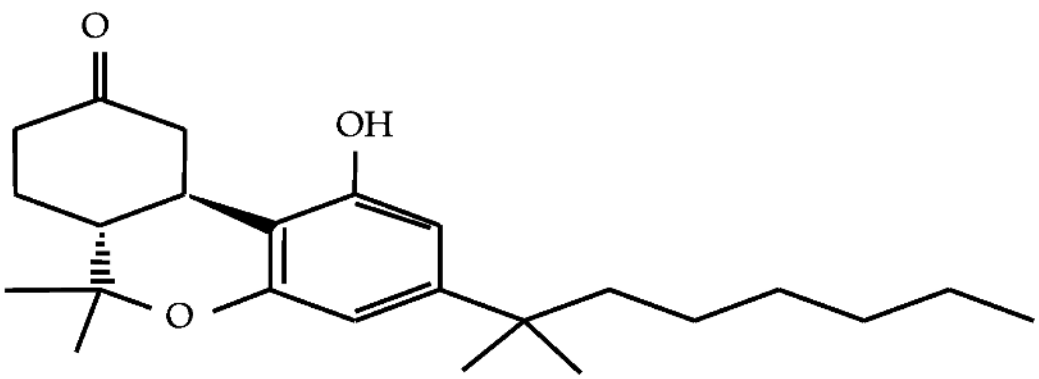
Further molecular modification results in the L-759,656 compound, which has a structural analogy to nabilone, but possesses a CB_2 receptor affinity bias of slightly over 1000-fold.[13]

Probably the most modified compounds of the "classical" type are HU-210 and HU-211, which are the less labile Δ^8-THC isomer. The design of these compounds employed the best combination of known structure-activity relationship (SAR) parameters into a pair of molecules that differ only in their enantiomeric configuration. However, this difference results in HU-210 being optimized for the cannabinoid neuronal (CB_1) receptor and the most powerful psychoactive cannabinoid yet discovered. In contrast, HU-211 ("dexanabinol") is completely devoid of these properties (see Chapter 36).

Nonclassical

Nonclassical cannabinoids include molecules that have a more radical rearrangement of, addition to, or deletion from the prototypical structures, or have an isosteric replacement of an atomic substituent.[8,21] These changes are often combined with the more subtle modifications of the classical com-

FIGURE 2.2. Nabilone



pounds. However, sometimes entirely unrelated molecular structures (i.e., indoles) seem to fit the receptor effectively.

Levonantradol (see Figure 2.3), a parenteral nonclassical cannabinoid, was probably the most successful cannabinoid drug to emerge from the Pfizer laboratories, although it was not approved for use due to an undesirable side-effect profile.[19]

Various configurations involving an elimination of the "B" ring, or cyclic additions to the classic THC structure have been attempted with various degrees of success. The most well-known of the former compounds (see Figure 2.4) is CP-55,940,[21] which has become a widely used standard agonist for the testing of cannabinoid receptor affinity.

WIN-55,212-2 represents the most radical departure from the classical cannabinoid structure and is a multiring compound having an indole nu-

FIGURE 2.3. Levonantradol

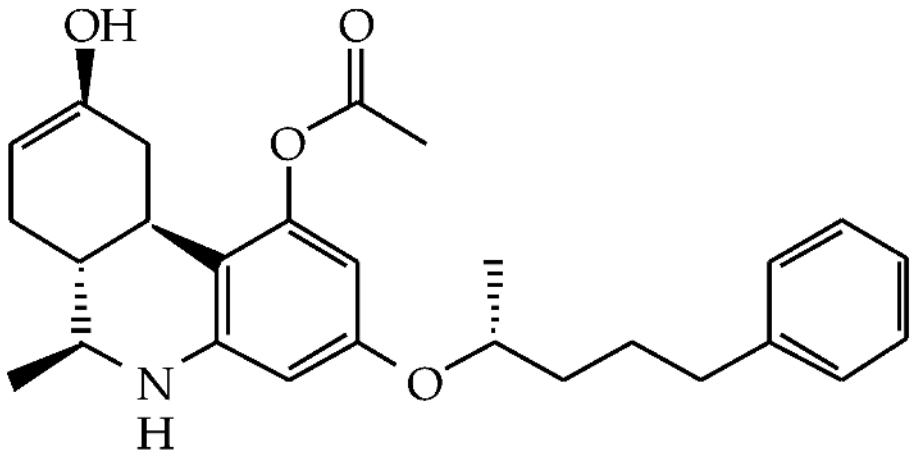
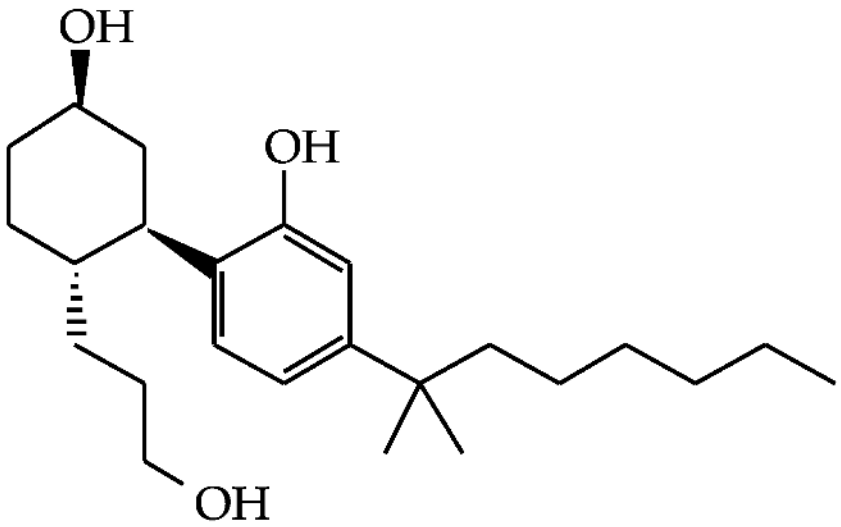


FIGURE 2.4. CP-55,940



cleus. Its structure (see Figure 2.5A) is a variation on the nonsteroidal anti-inflammatory analgesic[14] known as pravadoline (see Figure 2.5B), which possesses cannabinoid-like antinociceptive properties. Although WIN-55,212-2 was initially thought to bind to the CB_1 receptor, it actually has a seven-fold bias towards the CB_2 receptor.[29]

ANANDAMIDE CONGENERS

Endocannabinoids

For ease of reference, endocannabinoids can be conveniently divided into three regions (see Figure 2.6) in the manner suggested by Walpole and colleagues[32] for their structurally similar capsaicin analogues. In addition to anandamide or arachidonylethanolamide (see Chapter 7) two additional major endocannabinoids were detected, 2-arachidonylglycerol (2-AG) and palmitylethanolamide (PEA). The endocannabinoid 2-AG is an incompletely hydrolyzed triglyceride ester of arachidonic acid, PEA being a shorter and completely saturated fatty acid derivative (see Figure 2.6).

Three other minor anandamides, whose structures are based on docosatetraenoic, homo-γ-linolenic and mead acids, respectively, were subsequently found.

Synthetic Analogues

Abadji and colleagues[1] first synthesized a series of arachidonylethanolamide analogues bearing a methyl on the chiral alkylamide carbon located either *alpha* or *beta* to the amide nitrogen. The (*R*)-(+)-α-methanandamide

FIGURE 2.5. WIN-55,212-2 (A) and Pravadoline (B)

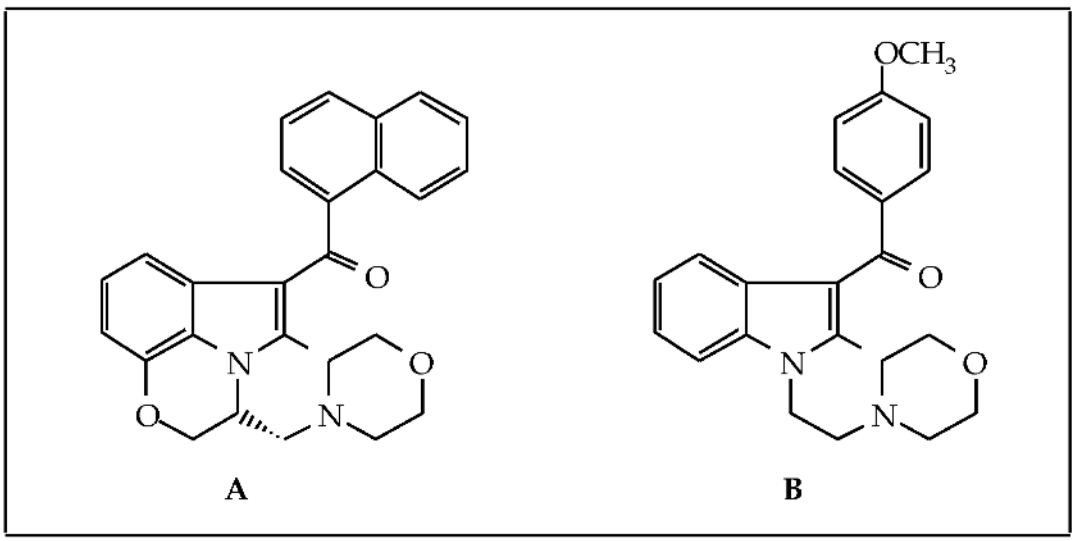
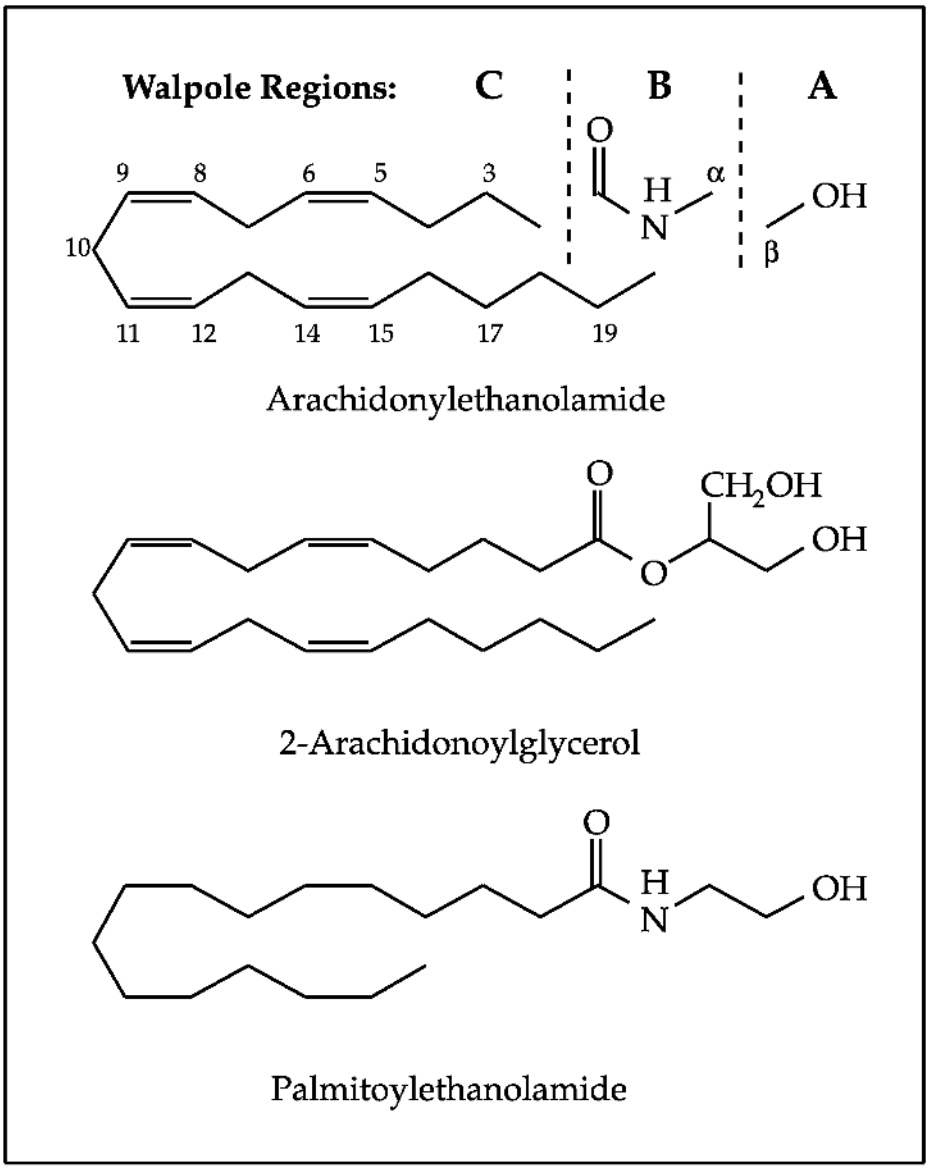


FIGURE 2.6. Major Endocannabinoids



was found to possess both a fourfold higher affinity for the CB_1 receptor and a greater catabolic resistance, when compared to the native species. Others subsequently reported additional synthetic anandamide congeners that were modified with various enzyme-blocking alkyl groups at the *alpha* carbon of the alkylamide or at C-2 of the fatty acid.[28] Replacement of the terminal hydroxy moiety by, e.g., fluorine, as well as the use of other fatty acids, were explored.[28] Based on the SAR of THC C-3 homologue modifications, a number of analogous fatty acid chain lengthening and branching strategies were attempted (e.g., see the work of Ryan and colleagues[27]). These changes succeeded in producing compounds with considerably greater receptor affinity, if not always more pharmacological activity.

Amidase Inhibitors

Fatty acid-based compounds have been synthesized (see Figure 2.7) that mimic the structure of anandamide, but act as inhibitors of the catabolic amidase enzyme, also known as "amidohydrolase" and more recently[11] under the broader term "fatty acid amide hydrolase" (FAAH). Most of these compounds are apparently inactive at the CB_1 receptor. Exceptions include arachidonyl trifluoromethylketone (Arach-F_3), which has a CB_1 receptor affinity that is 15 to 40-fold less than that of AEA, and methyl-arachidonyl fluorophosphonate (MAFP), which is approximately twice as potent as AEA, although it is also a thousand-fold more efficient than Arach-F_3 as an amidase inhibitor.[10]

The amidase inhibitor, 2-Octyl-γ-bromoacetoacetate,[34] also known as 1-methyl-heptyl-γ-bromo-acetoacetate (see Figure 2.8), is found in neural fluids.[23] It is intriguing to speculate on whether its ability to induce sleep[31] is due to a direct receptor mechanism or caused indirectly via AEA accumulation. Lipoxygenase products of anandamide are reported to act on this enzyme in a similar fashion.[18] Structurally unrelated synthetic amidase inhibitors, e.g., bromomethylene-tetrahydro-naphthalenylpyranone (BTNP) and *para*-methyl sulfonyl fluoride (PMSF), have also been described.[4,7]

FIGURE 2.7. Some Aliphatic Amidase Inhibitors

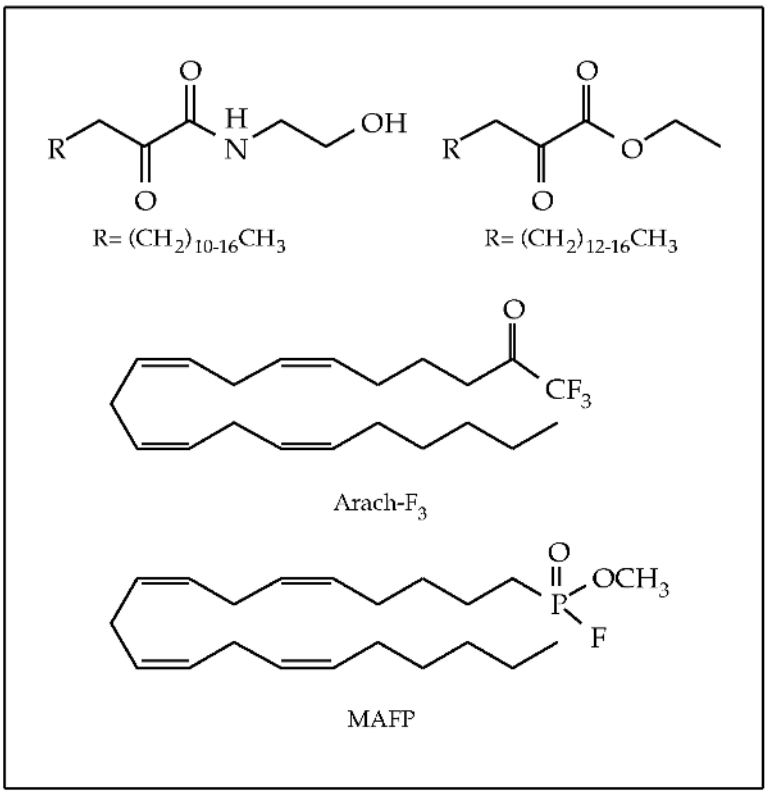
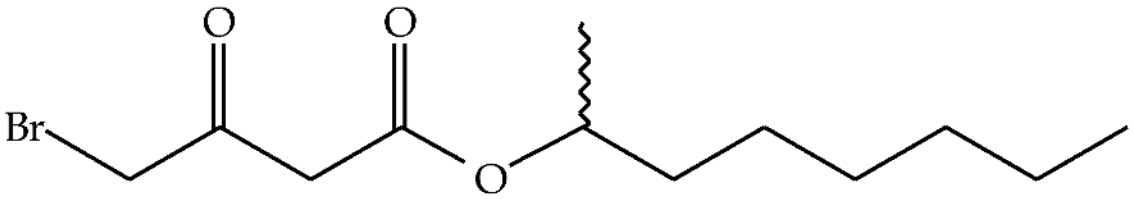


FIGURE 2.8. 1-Methyl-Heptyl-γ-Bromo-Acetoacetate



A regulation of AEA levels via FAAH may also be engendered through an "entourage" effect,[20] whereby various fatty acid-based products, e.g., oleamide,[9] inactive at the CB_1 or CB_2 receptor site, compete with AEA for this nonspecific enzyme.

AM-404 (see Figure 2.9) is a synthetic fatty amide that acts as a selective inhibitor of anandamide transport but is not a significant cannabinoid receptor ligand. It prevents cellular re-uptake of anandamide[5] thereby preventing its catabolism by the membrane-bound enzyme.

RECEPTOR ANTAGONISTS

The first antagonist of a cannabinoid receptor binding site was announced by Rinaldi-Carmona and colleagues[25] as the potent and orally active CB_1-selective compound, SR 141716A (see Figure 2.10A). A corresponding CB_2 receptor antagonist, SR 144528 (see Figure 2.10B), was discovered by the same group.[26] This latter, orally active compound is claimed to be highly specific and have a 700-fold affinity bias for the CB_2 versus CB_1 receptor.

Compounds of this pharmacological class may eventually show potential as future medicines; e.g., as memory enhancers[30] or possibly as anorexics. However, their immediate utility, when accompanied by various receptor agonists and an array of enzyme inhibitors, is as innovative pharmacological tools for exploration of cannabinoid receptor systems.

FIGURE 2.9. AM-404

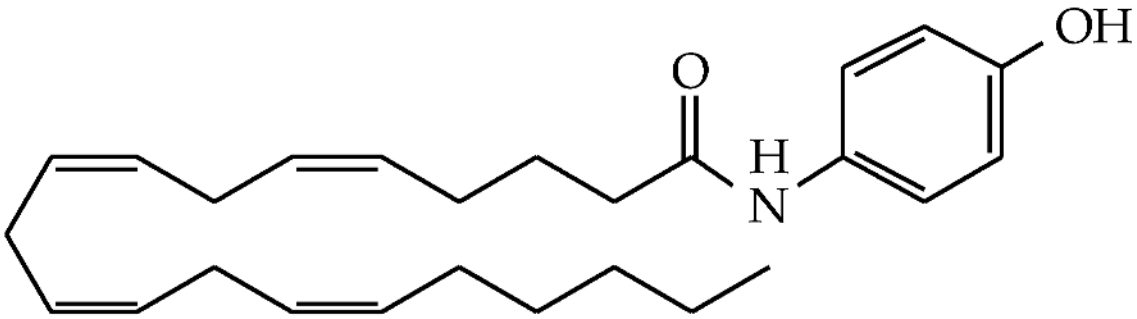
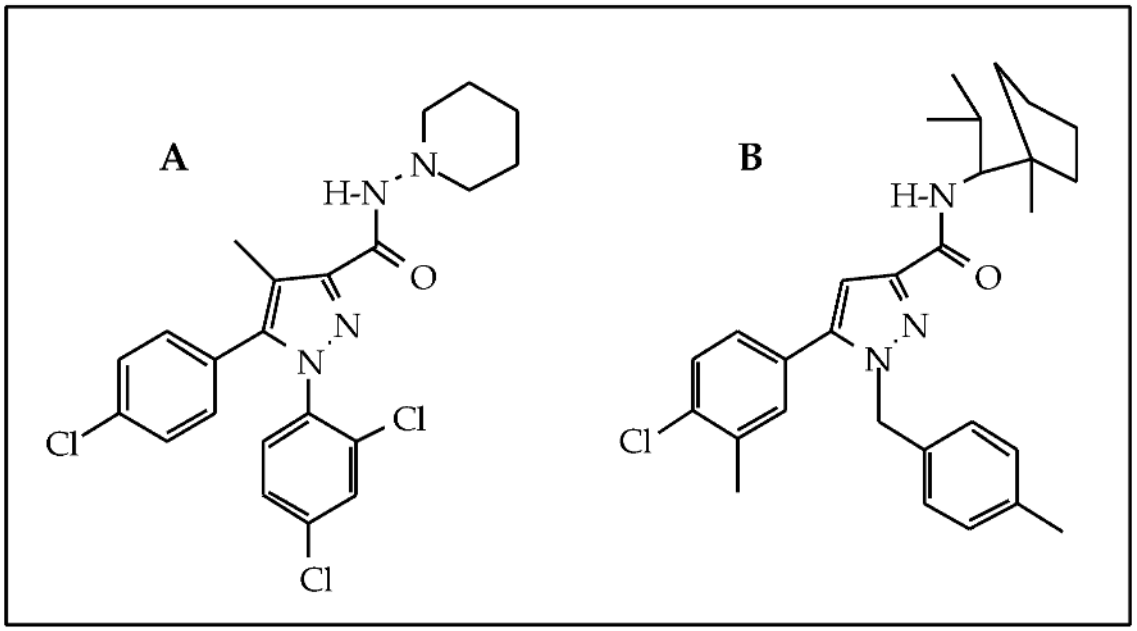


FIGURE 2.10. SR 141716A (A) and SR 144528 (B)



REFERENCES

1. Abadji V, Lin S, Gihan T, Griffen G, Stevenson LA, Pertwee GR, Makriyannis A. (*R*)-methanandamide: A chiral novel anandamide possessing higher potency and metabolic stability. *Journal of Medicinal Chemistry* 1994;37(12):1889-1893.

2. Adams R, Loewe S, Jelinek C, Wolff H. Tetrahydrocannabinol homologs with marihuana activity. IX. *Journal of the American Chemical Society* 1941;63:1971-1976.

3. Archer RA, Stark P, Lemberger L. Nabilone. In Mechoulam R, ed. *Cannabinoids As Therapeutic Agents*. Boca Raton, FL: CRC Press, 1986, pp. 85-103.

4. Beltramo M, di Tomaso E, Piomelli D. Inhibition of anandamide hydrolysis in rat brain tissue by (*E*)-6-(bromomethylene) tetrahydro-3-(1-naphthalenyl)-2H-pyran-2-one. *FEBS Letters* 1997;403(3):263-267.

5. Beltramo M, Stella N, Calignano A, Lini SY, Makriannis A, Piomelli D. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. *Science* 1997;277(532g):1094-1096.

6. Ben-Zvi Z, Mechoulam R, Burstein S. Identification through synthesis of an active *delta*-1(6)-tetrahydrocannabinol metabolite. *Journal of the American Chemical Society* 1970;92(11):3468-3469.

7. Childers SR, Sexton T, Roy MB. Effects of anandamide on cannabinoid receptors in rat brain membranes. *Biochemical Pharmacology* 1994;47:711-715.

8. Compton DR, Martin BR. The effect of the enzyme inhibitor phenylmethylsulfonyl fluoride on the pharmacological effect of anandamide in the mouse model of cannabimimetic activity. *Journal of Pharmacology and Experimental Therapeutics* 1997;283(3):1138-1143.

9. Cravatt B, Prospero-Garcia O, Siuzdak G, Gilula NB, Henriksen SJ, Boger DL, Lerner RA. Chemical characterization of a family of brain lipids that induce sleep. *Science* 1995;268:1506-1509.

10. Deutsch DG, Omeir R, Arreaza G, Salehani D, Prestwich GD, Huang Z, Howlett A. Methyl arachidonyl fluorophosphonate: A potent irreversible inhibitor of anandamide amidase. *Biochemical Pharmacology* 1997;53(3):255-260.

11. Di Marzo V. "Endocannabinoids" and other fatty acid derivatives with cannabimimetic properties: Biochemistry and possible physiopathological relevance. *Biochimica et Biophysica Acta* 1998;1392(2-3):153-175.

12. Gaoni Y, Mechoulam R. Hashish. IX. Concerning the isomerization of Δ^1- to $\Delta^{1(6)}$-tetrahydrocannabinol. *Journal of the American Chemical Society* 1966;88:5673-5675.

13. Gareau Y, Dufresne C, Gallant M, Rochette C, Sawyer N, Slipetz DM, Trembley N, Weech PK, Metters KM, Labelle M. Structure-activity relationships of tetrahydrocannabinol analogues on human cannabinoid receptors. *Bioorganic Medicinal Chemistry Letters* 1996;6:189-194.

14. Haubrich DR, Ward SJ, Baizman E, Bell MR, Bradford J, Ferrari R, Miller M, Perrone M, Pierson AK, Saelens JK, Luttinger D. Pharmacology of pravadoline: A new analgesic agent. *Journal of Pharmacology and Experimental Therapeutics* 1990;255(2):511-522.

15. Hollister, LE. Structure-activity relationships in man of *Cannabis* constituents, and homologues and metabolites of Δ^9-tetrahydrocannabinol. *Pharmacology* 1974;11(1):3-11.

16. Hollister LE, Gillespie HK. *Delta*-8- and *delta*-9-tetrahydrocannabinol. *Clinical Pharmacology and Therapeutics* 1973;14(3):353-357.

17. Hollister LE, Richards RK, Gillespie HK. Comparison of tetrahydrocannabinol and synhexyl in man. *Clinical Pharmacology and Therapeutics* 1968;9(6):783-791.

18. Maccarrone M, van der Stelt M, Rossi A, Veldink GA, Vliegenthart JFG, Agro AF. Anandamide hydrolysis by human cells in culture and brain. *Journal of Biological Chemistry* 1998;273(48): 32332-32339.

19. Mechoulam R, Feigenbaum JJ. Towards cannabinoid drugs. In Ellis GP, West GB eds., *Progress in medicinal chemistry,* Volume 24. Amsterdam: Elsevier Science Publishers (Biomedical Division), 1987, pp. 159-207.

20. Mechoulam R, Fride E, Di Marzo V. Endocannabinoids. *European Journal of Pharmacology* 1998;359(1): 1-18.

21. Melvin LS, Milne GM, Johnson MR, Subramaniam B, Wilken GH, Howlett AC. Structure-activity relationships for cannabinoid receptor-binding and analgesic activity: Studies of bicyclic cannabinoid analogs. *Molecular Pharmacology* 1993;44(5):1008-1015.

22. Pate DW. The Phytochemistry of *Cannabis:* Its ecological and evolutionary implications. In Ranalli P. ed., *Advances in hemp research.* Binghamton, NY: The Haworth Press, 1999, pp. 243-255.

23. Patricelli MP, Patterson JE, Boger DL, Cravatt BF. An endogenous sleep-inducing compound is a novel competitive inhibitor of fatty acid amide hydrolase. *Bioorganic Medicinal Chemistry Letters* 1998;8:613-618.

24. Razdan RK. Structure-activity relationships in cannabinoids. *Pharmacological Reviews* 1986;38(2):75-149.

25. Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, et al. SR 141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Letters* 1994;350(2-3):240-244.

26. Rinaldi-Carmona M, Barth F, Millan J, Derocq J-M, Casellas P, Congy C, Oustric D, Sarran M, Bouaboula M, Calandra B, et al. SR 144528, the first potent and selective antagonist of the CB_2 cannabinoid receptor. *Journal of Pharmacology and Experimental Therapeutics* 1998;284(2):644-650.

27. Ryan WJ, Banner WK, Wiley JL, Martin BR, Razdan RK. Potent anandamide analogs: The effect of changing the length and branching of the end pentyl chain. *Journal of Medicinal Chemistry* 1997;40(22):3617-3625.

28. Sheskin T, Hanus L, Slanger J, Vogel Z, Mechoulam R. Structural requirements for binding of anandamide-type compounds to the brain cannabinoid receptor. *Journal of Medicinal Chemistry* 1997;40(5):659-667.

29. Showalter VM, Compton DR, Martin BR, Abood ME. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB_2): Identification of cannabinoid receptor subtype selective ligands. *Journal of Pharmacology and Experimental Therapeutics* 1996;278(3):989-999.

30. Terranova J-P, Storme J-J, Lafon N, Perio A, Rinaldi-Carmona, Le Fur G, Soubrie P. Improvement of memory in rodents by the selective CB_1 cannabinoid receptor antagonist, SR 141716. *Psychopharmacology* 1996;126(2):165-172.

31. Torii S, Mitsumori K, Inubushi S, Yanagisawa I. The REM sleep-inducing action of a naturally occurring organic bromine compound in the *encephale isolé* cat. *Psychopharmacologia* 1973;29(1):65-75.

32. Walpole CSJ, Wrigglesworth R, Bevan S, Campbell EA, Dray A, James IF, Perkins MN, Reid DJ, Winter J. Analogues of capsaisin with agonist activity as novel analgesic agents; Structure-activity studies. 1. The aromatic "A-region." *Journal of Medicinal Chemistry* 1993;36:2362-2372.

33. Ward A, Holmes B. Nabilone. A preliminary review of its pharmacological properties and therapeutic use. *Drugs* 1985;30(2):127-144.

34. Yanagisawa I, Yoshikawa H. A bromine compound isolated from human cerebrospinal fluid. *Biochimica et Biophysica Acta* 1973;329(2):283-294.

Chapter 3

Chemical Constituents of *Cannabis*

Mahmoud A. ElSohly

The cannabis plant (*Cannabis sativa* L.) is one of the oldest medicinal plants known, and the use of cannabis preparations can be traced back over five thousand years.[1]

The same preparations once accepted as therapeutically useful drugs have been considered as innocuous drugs of leisure in most countries. The rapid increase in the use and abuse of these preparations resulted in the control of cannabis and its crude drug products via international treaties.[12]

Perhaps the issue of the medical utility of cannabis has never been as controversial as it is today, particularly in the United States. Although the drug is still federally classified under Schedule I in the Controlled Substances Act of 1970, several states (California, Arizona, Washington, etc.) have passed laws permitting the possession, cultivation, and use for medicinal purposes. One of the contributing factors to the continued prohibition of cannabis is the fact that for a long time the general opinion held by the majority of the scientific community is that cannabis preparations (such as marijuana) can be evaluated solely on the (-)-Δ^9- tetrahydrocannabinol (Δ^9-THC) content, to the neglect of other cannabinoids and chemicals in the crude drug. In fact, synthetic Δ^9-THC was referred to as "synthetic marijuana" by many.

The time has come to correct this gross misrepresentation and to provide a complete account of the chemical constituents of cannabis and what it means to use the crude drug marijuana, particularly in the smoked form, as a medicine in terms of its chemical complexity.

Investigations into the chemistry of cannabis and the identification of its active constituent(s) can be traced back to the nineteenth century. In fact, the active constituent was thought for a long time to be an alkaloid. It was not until 1964 when the correct chemical structure of Δ^9-THC (also known as Δ^1-THC; see Chapter 2) was determined by Gaoni and Mechoulam.[2] This

marked the beginning of an intensive search for other constituents of the cannabis plant, and today a total of 483 natural components have been isolated and/or identified (see Table 3.1). In this chapter a brief overview of the different types of constituents known to exist in *Cannabis sativa* L. will be presented.

TABLE 3.1. *Cannabis* Constituents

Chemical Class	Known
Cannabinoids	66
Nitrogenous compounds	27
Amino acids	18
Proteins, glycoproteins, and enzymes	11
Sugars and related compounds	34
Hydrocarbons	50
Simple alcohols	7
Simple aldehydes	12
Simple ketones	13
Simple acids	21
Fatty acids	22
Simple esters and lactones	13
Steroids	11
Terpenes	120
Noncannabinoid phenols	25
Flavonoids	21
Vitamins	1
Pigments	2
Elements	9
TOTAL	483

CHEMICAL CONSTITUENTS

For a complete listing of the individual chemical constituents of the cannabis plant, the readers are referred to two comprehensive review articles published in 1980[10] and 1995[7] which contain approximately three hundred references. *Cannabis* constituents can be classified into the following distinct chemical classes:

Cannabinoids—66 Known

Cannabinoids are the most distinctive and specific class of compounds known to exist only in the cannabis plant and, hence, their name. Several subclasses of cannabinoids have been identified. These are:

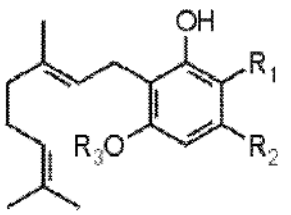
Cannabigerol (CBG) type. There are six CBG-related cannabinoids known (see Figure 3.1). CBG itself was the first cannabinoid identified,[3] and its acid precursor (CBGA) was shown to be the first biosynthetic cannabinoid formed in the plant.[9] Other members of the CBG group include the C3 side chain homologues and the mono-methyl ether derivative (see Figure 3.1).

Cannabichromene (CBC) type. A total of five CBC- related cannabinoids have been identified, mainly with C5, and to a much lesser extent, with C3 side chains (see Figure 3.2).

Cannabidiol (CBD) type. Seven CBD-related cannabinoids have been identified with side chains containing 1, 3, 4, or 5 carbons, the latter being the most predominant. As is the case with other cannabinoids, the acid precursors of CBD and its C3 homologue have been isolated with the C5 acid being the first cannabinoid acid discovered in 1955[5] (see Figure 3.3).

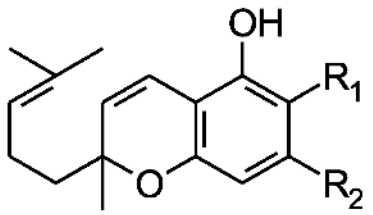
Delta-9-Tetrahydrocannabinol (Δ^9-THC) type. A total of nine cannabinoids in this group have been identified with side chains of 1, 3, 4, and 5 carbons. The precursor acids for all compounds are known with the major component being the acid A of the C5 homologue. The acid B of Δ^9-THC has been isolated where the COOH group is located on the 4 position of the

FIGURE 3.1. Cannabigerol Type



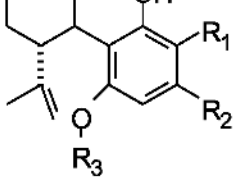
R_1 = H or COOH
R_2 = C_3 or C_5 side chain
R_3 = H or CH_3

FIGURE 3.2. Cannabichromene Type



R_1 = H or COOH
R_2 = C_3 or C_5 side chain

FIGURE 3.3. Cannabidiol Type



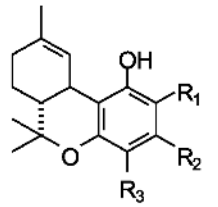
R_1 = H or COOH
R_2 = C_1, C_3, C_4, or C_5 side chain
R_3 = H or CH_3

aromatic ring as opposed to the C2 in acid A. Δ^9-THC is considered to be the most psychologically active cannabinoid in the plant material. However, its acid precursor is not psychologically active (see Figure 3.4).

Delta-8-Tetrahydrocannabinol (Δ^8-THC) type. Only Δ^8-THC and its acid precursor belong to this group. They are considered to be artifacts through migration of the double bond from the 9, 10 position to the more thermodynamically stable 8, 9 position. Δ^8-THC has approximately 80 percent of the activity of Δ^9-THC (see Figure 3.5).

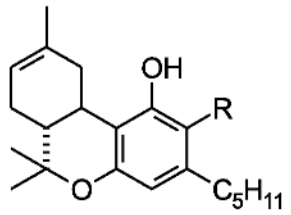
Cannabinol and cannabinodiol types. These are the fully aromatized derivatives of THC and CBD, respectively. Although these compounds have been isolated from different cannabis cts, they are thought of as artifacts resulting from the air oxidation of the respective parent compounds. For example, the concentration of CBN in cannabis products (marijuana, hashish, and hash oil) increases during storage of these materials at the expense of reduction in the Δ^9-THC concentration, albeit not to the same degree. A mechanism for such conversion has been proposed[11] which involves several polyhydroxylated intermediates. An empirical formula based on the concentration of CBN relative to Δ^9-THC was used by Ross and ElSohly[6] to determine the age of the plant material (see Figures 3.6 and 3.7).

FIGURE 3.4. Δ^9-*trans*-Tetrahydrocannabinol Type



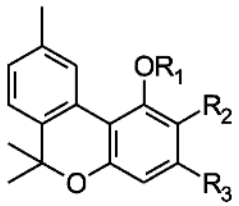
R_1 or R_3 = H or COOH
R_2 = C_1, C_3, C_4, or C_5 side chain

FIGURE 3.5. Δ^8-*trans*-Tetrahydrocannabinol Type



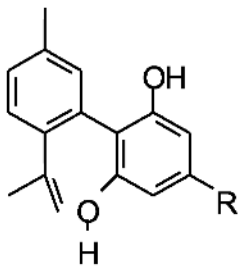
R = H or COOH

FIGURE 3.6. Cannabinol Type



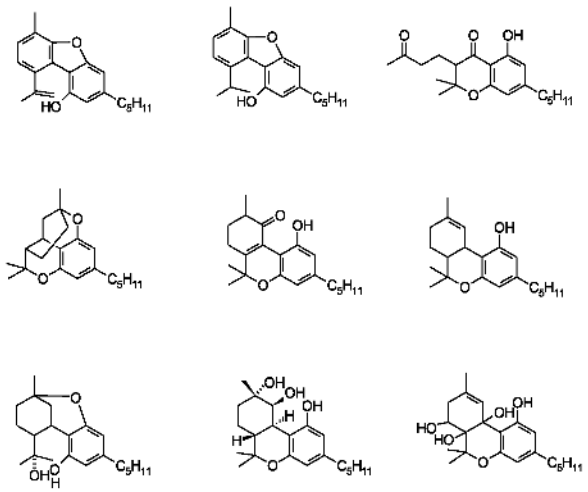
R_1 = H or C_3
R_2 = H or COOH
R_3 = C_1, C_3, C_4, or C_5 side chain

FIGURE 3.7. Cannabinodiol Type



R = C_3 or C_5 side chain

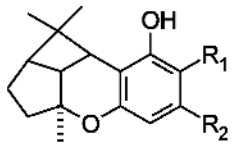
FIGURE 3.8. Miscellaneous Cannabinoids



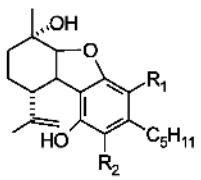
Other cannabinoids. These belong to the cannabicyclol type (three known), cannabielsoin type (five known), cannabitriol type (nine known) and a miscellaneous type (eleven known).

Other cannabinoid types (see Figure 3.8).

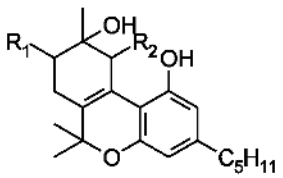
Cannabicyclol (CBL) type



Cannabielsoin type



Cannabitriol type

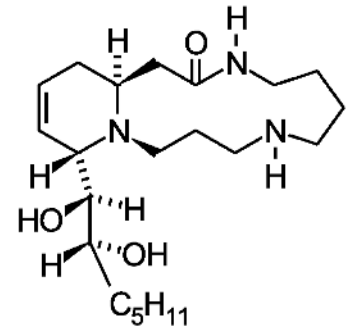


Nitrogenous Compounds—27 Known

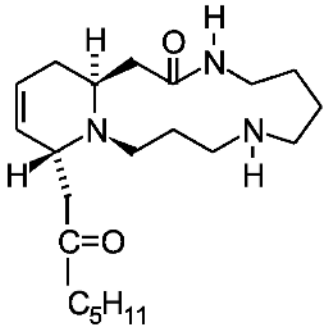
The nitrogenous compounds include five quaternary bases, 8 amides of which 5 are lignanamides, 12 simple amines, and 2 spermidine type alkaloids named cannabisativine and anhydrocannabisativine (see Figure 3.9).

FIGURE 3.9. Spermidine Alkaloids

cannabisativine



anhydrocannabisativine



Amino Acids—18 Known

Amino acids are common in all plants including cannabis. The only amino acids not reported in cannabis are cystine, asparagine, glutamine, hydroxyproline, and hydroxylysine.

Proteins, Glycoproteins, and Enzymes—11 Known

Three proteins (edestin, zeatin, and zeatinnucleoside), six enzymes (edestinase, glucosidase, polyphenol oxidase, peptidase, peroxidase, and adenosine-5-phosphatase), and two glycoproteins of unknown structure make up the group.

Sugars and Related Compounds—34 Known

This group is composed of 13 monosaccharides, 2 disaccharides, 5 polysaccharides, 12 cyclitols, and 2 amino sugars, all common in the plant kingdom.

Hydrocarbons—50 Known

The hydrocarbons found in cannabis are primarily straight chain hydrocarbons ranging from C9 to C39 with a few branched hydrocarbons in which one or two methyl groups form substituents along the main chain.

Simple Alcohols, Aldehydes, Ketones, and Acids

There are seven simple aliphatic alcohols ranging from C1–C16; 12 simple aldehydes (C2–C13) of which only one is aromatic (*p*-ethylbenzaldehyde); 13 simple aliphatic ketones (C3–C18); and 21 simple acids distributed between aliphatic and aromatic, with only one inorganic acid (phosphoric), which have been identified in cannabis.

Fatty Acids—22 Known

The fixed oils of cannabis seeds or hemp seeds have been promoted in health food stores as a good source for polyunsaturated fatty acids (see Chapter 38). Today a total of 22 different fatty acids have been identified, the most abundant of which are linoleic, oleic, stearic, and palmetic acid. Recent work in our laboratories[8] showed no significant difference in the fatty acid composition of the oil generated from drug or hemp (fiber) type seeds.

Simple Esters and Lactones

Twelve esters and one lactone have been identified in cannabis. The esters are mainly low molecular weight organic acids, with two methyl esters of the fatty acids palmetic and linoleic. There is one aromatic acid ester (methyl salicylate). The only lactone is 2-C-methyl-aldoteronolactone.

Steroids

Eleven phytosterols were identified in cannabis belonging to the stigmasterol, β-sitosterol, compesterol, and ergosterol types.

Terpenes

A total of 120 different terpenes have been identified in cannabis belonging mainly to the mono- and sesquiterpene groups, with only one diterpene and two triterpenes. The terpenes are those constituents responsible for the flavor of the different varieties of cannabis and determine the preference by the cannabis users of one variety versus another. They have no contribution however, to the psychological activity of the drug.

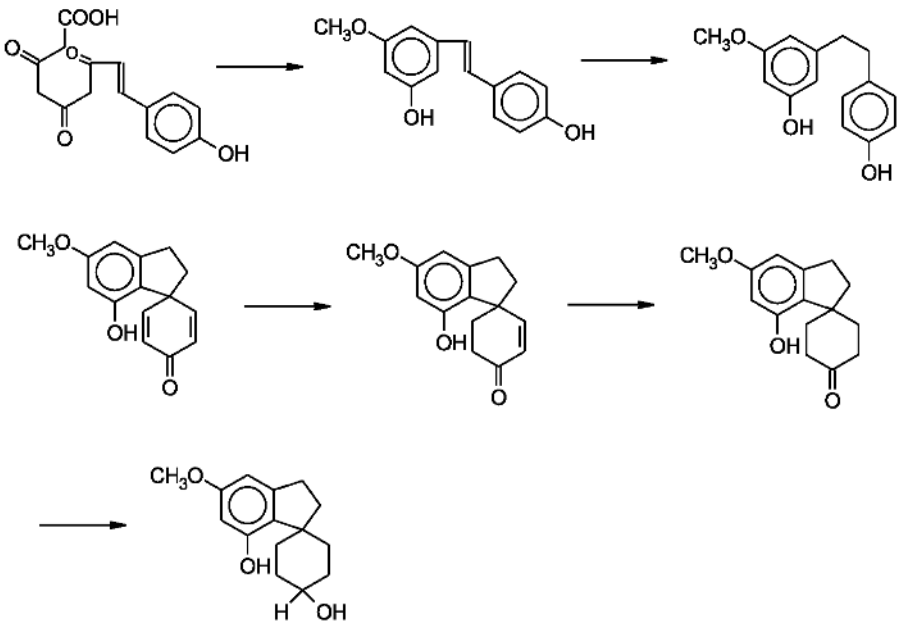
Noncannabinoid Phenols

Twenty-five noncannabinoid (also nonflavonoid) phenols were identified in cannabis. These range from simple phenols such as eugenol and related phenols and its methylester, to dihydrostilbenes and dihydrophenanthrenes to spiroindans. The dihydrostilbenes and spiroindans are closely related, and they possibly have the same biosynthetic origin as shown in the diagram (see Figure 3.10). The spiroindans have only been detected in cannabis.

Flavonoids

Twenty-one flavonoids have been reported in cannabis, mainly as the O-glycosides of the C-glycosides orientin, vitexoin, and isointexin, and the O-glycosides of the flavonoids apigenin, luteolin, quercetin, and kaemp-

FIGURE 3.10. Proposed Outline for the Biosynthetic Formation of the Spiroindans and Dihydrostilbenes of *Cannabis*



ferol. The exact structure, including the linkage of these compounds has not been fully determined, and most identifications are based on characterization of the hydrolysis products.

Vitamins and Pigments

One vitamin (vitamin K) and two pigments (carotene and zanthophylls) have been reported in cannabis.

Elements

Nine elements were reported to be present in cannabis. These are Hg, Zn, Mn, Cu, Fe, Mg, Ca, K, and Na.

CONCLUSION

The cannabis plant and the crude drug products thereof (marijuana, hashish, and hash oil) are complex natural products with a wide variety of chemical constituents. As shown in this chapter, there are 483 different identifiable chemical constituents known to exist in cannabis. The suggestion that the crude drug marijuana should be approved as medicine, particularly in the smoked form, goes against scientific judgment when one considers the tremendous number of components to be ingested from such a product. Although Δ^9-THC and other cannabinoids, and possibly other constituents as

pure chemical entities, might be useful medicaments for specific indications, smoked marijuana should not be used as a substitute. In this regard, I would like to reiterate a statement from the Preface of the U.S. Institute of Medicine's report, *Marijuana and Medicine:* "the report concludes that the future of cannabinoid drugs lies not in smoked marijuana but in chemically defined drugs that act on the cannabinoid systems that are a natural component of human physiology."[4]

REFERENCES

1. Farnsworth NR. Pharmacognosy and chemistry of *Cannabis sativa. Journal of the American Pharmaceutical Association* 1969;N59:410.

2. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society* 1964;86:646-647.

3. Gaoni Y, Mechoulam R. The structure and synthesis of cannabigerol, a new hashish constituent. *Proceedings of the Chemical Society* 1964;82.

4. Institute of Medicine. Preface ix. In Joy JE, Benson JA, Watson SJ, eds., *Marijuana and medicine: Assessing the science base*. Washington, DC: Institute of Medicine, National Academy Press, 1999.

5. Krejci Z, Santavy F. Isolace dalsich latek Z listi indick eho konopi cannabis sativa L. *Acta Universitatis Palackiana Olomucensis Facultatis Medicae* 1955;6:59.

6. Ross S, ElSohly MA. CBN and Δ^9-THC concentration ratio as an indicator of the age of stored marijuana samples. *Bulletin on Narcotics* 1998; XLIX and L(1/2): 139-147.

7. Ross S, ElSohly MA. Constituents of *Cannabis sativa* L. XXVIII. A review of the natural constituents: 1980-1994. *Zagazig Journal of Pharmaceutical Sciences* 1995;4(2):1-10.

8. Ross SA, ElSohly HN, ElKashoury EA, ElSohly MA. Fatty acids of cannabis seeds. *Phytochemical Analysis* 1996;7:279-283.

9. Shoyama Y, Yagi M, Nishioka I, Yamauchi T. Biosynthesis of cannabinoid acids. *Phytochemistry* 1975;14:2189.

10. Turner C, ElSohly MA, Boeren E. Constituent of *Cannabis sativa* L. XVII. A review of the natural constituents. *Journal of Natural Products* 1980;43(2):169-234.

11. Turner CE, ElSohly MA. Constituents of *Cannabis sativa* L. XVI. A possible decomposition pathway of Δ^9-tetrahydrocannabinol to cannabinol. *Journal Heterocyclic Chemistry* 1979;16:1667-1668.

12. United Nations Single Convention on Narcotic Drugs signed at New York, NY, March 30, 1961.

Chapter 4

History of Cannabis in Western Medicine

Manfred Fankhauser

CANNABIS BEFORE THE BIRTH OF CHRIST

"Pharmacognosy (herbal medicine) is the mother of all natural disciplines."[13] At first consideration, this quote may seem exaggerated; however, plants have been used for therapeutic purposes since the beginning of human thought.

Central Asia seems to be the origin of the hemp plant. It is not possible to say exactly where and when cannabis came into existence as a medicinal plant. Fragments of reports occur centuries before the birth of Christ. The oldest reports about medicinal applications originate in China and Egypt. The well-known Chinese doctor Hua T'uo reportedly made use of a hemp and wine recipe called "Ma-yo" as an anesthetic for surgical operations.

Approximately 800 years before the birth of Christ, the plant appeared to have reached India. Due to its narcotic effect, cannabis was used in certain rituals and soon became established among Indian medicinals and narcotics. Even centuries later, cannabis retained its place in the Indian Ayurvedic medicine. Hemp was used, for example, against catarrh or as an anesthetic. Hemp had also been mentioned previously in a medicinal context in the Vedas, the oldest Indian religious texts.

Persian and Tibetan traditions of cannabis use also stem from before the birth of Christ. Even in the time of Buddha (500 B.C.), cannabis was allegedly used as an anesthetic to perform extraordinary surgery. Assyrian fragments of herbal literature are known dating back to the seventh

century B.C., in which precise medicinal applications for hemp products are described.

CANNABIS IN THE CLASSICAL ERA

Among the Greeks and Romans, cannabis was primarily employed as fiber, but perhaps also as a multipurpose medicine. A quote often cited is the scene described in Homer's *Odyssey* (4:219-232). Helena drops the medicine *Nepenthes* into the wine drank by Telemachus and his comrades, which provokes the forgetting of all pain. Homer wrote:

> And she added a potion to the wine that they were drinking, to calm pain and anger and to forget all sorrows. Whomsoever enjoyed this potion with the wine, would not shed a tear that day, no matter if his mother and father lay dead before him, no matter if his dear son or brother were slayed by the sword before his very eyes.[6]

It is considered possible that *Nepenthes* was a cannabis product, in whole or in part. However, some believe that the story is a literary invention. Even in ancient times speculation was widespread concerning the composition of *Nepenthes*.

The first appearance of cannabis as a medicine in an occidental language is in the medicinal writings of Dioscorides (ca. 50 A.D.):

> Cultivated hemp. Cannabis (some call it Cannabion, some Schoinostrophon, some Asterion) is a plant, of much use in this life for ye twisting of very strong ropes. It bears leaves like to the Ash, of a bad scent, long stalks, empty, a round seed, which being eaten of much doth quench geniture, but being juiced when it is green is good for the pains of the ears.[4]

In addition to Dioscorides, Galen was one of the most famous doctors of the classical era. He mentions hemp in two of his many writings. Along with benefits against flatulence and its stimulating effects he mentions that overuse of the seeds leads to stomachaches, headaches, and finally to impotence. The green juice of the seeds was recommended against earache. Despite concrete reports on the analgesic effect of the plant, its significance as a narcotic was apparently minor compared to opium.

With the fall of the old Roman empire, the Byzantine era began and with it the classic medicinal concepts of the ancients were carried over to the Arab world.

HASHISH IN THE ARABIC WORLD

The introduction of medicine from the classical civilizations into the Arabic-Islamic world really took place in the tenth century. The great authors of the past had been translated into Arabic and their medicinal knowledge had been integrated into the Arabic-Islamic linguistic and cultural arena, along with influences from India. More significance was placed on hashish as a medicinal and narcotic plant.

Many well-known Arabic doctors described medicinal uses of cannabis, especially Avicenna (ibn Sina). He mentions the plant in his work, *Canon of Medicine* (ca. 1000 A.D.). This medicinal oeuvre is often considered as the leading and most comprehensive medicinal treatise well into the fifteenth century. By this time, some scholars had already pointed out that misuse of hashish was evident in the culture.

In the thirteenth century the political fall of the Arabic-Islamic empire began along with a decline in Arabic-Oriental medicine which was later recognized as the essential basis for scholastic medicine in the western Middle Ages.

HEMP IN CENTRAL EUROPE

Cannabis, especially the seeds, was held in high regard in Europe of the Middle Ages. Herb gatherers differentiated between "fertilized" (cultivated) hemp which can, for example, be used against coughing and jaundice, and "mediocre" hemp as a substance utilized for arthritis, lumps, and other "hard tumors." The "Capitulare de villis" and the "Breviarium" by Charlemagne report on the cultivation of hemp at the end of the eighth century. Circa 1150 the German abbess Hildegard von Bingen describes hemp extensively in her medical work *Physica:*

> About Hemp—Cannabus
> Hemp is hot. It grows when the air is neither very hot nor very cold and so is its nature. Its seed is salubrious, and good as treat for healthy people. It is gentle and profitable in the stomach, since it removes the slime within and can be digested easily, reduces the bad juices and reinforces the strong ones. Whoever has an empty brain and head pains may eat it and the head pains will be reduced. Though he who is healthy and full of brains shall not be harmed by it. – He who has an empty brain shall be caused pain by indulging in hemp. A healthy head and a full brain will not be harmed. A towel prepared out of hemp laid upon sores and wounds works well since warmth is contained within it.[12]

In the centuries that followed, hemp was mentioned in most herbal and medicinal books, although Pope Innocent VIII forbade herbal healers from use of cannabis in the year 1484, dictating that hemp was an unholy sacrament of satanic rituals. This was the same year that the herbal book *Der Herbarius* appeared, which also listed hemp. Paracelsus described cannabis in a number of his many works. The well-known herbal books of the German authors Otto Brunfels, Hieronymus Bock, and Leonard Fuchs tell us nothing new about cannabis, but the plant is beautifully illustrated in the form of wood cuttings (see Figure 4.1). The same applies to Jacobus Theodorus Tabernaemontanus, who also mentions the application of the hemp root for the fabrication of gunpowder. The Italian Andreas Matthioli wrote in the *New Kräuterbuch*:[8]

> Den Weibern/so von wegen auffstossenden Mutter
> hinfallen/sol man angezündeten hanff für die Nasen halten/
> so stehen sie bald widerumb auff.
>
> [In Old German, Matthioli recommends holding smouldering hemp under the noses of patients in cases of an unclear women's disease.]
>
> Die hanffwurtzel in Wasser gesotten/
> Und obergeschlagen/erweicht die starzende
> Gewerbe oder Glieder/dienet auch wider
> Das Podogra [=Gussgicht].
>
> [He recommends cataplasms with hemp roots ("soaked and softened in water") against diseases of the limbs (arthritis?) and "Podagra" (old term for gout). The term *starzende Gewerbe* is unclear and may describe diseases of soft tissue (ulcers?).]

Interest in herbal books waned over the course of the seventeenth century. During the Enlightenment a search began for new therapeutic methods. Chemical substances were gradually establishing their place in the field of therapy.

CANNABIS IN EUROPEAN MEDICINE OF THE EIGHTEENTH CENTURY

In the eighteenth century, as in the preceding epochs, it was primarily the seeds of the medicinal plant *Cannabis sativa* that were used in the form of an oil or emulsion. Hemp oil was applied either as a cure against a number of illnesses (measles,[14] chicken pox,[14] inflammations of the breast,[2] gonorrhea,[15] cough,[9] stitch,[9] jaundice,[9] worms,[9] to mention but a few) or as a pharmaceutical vehicle, e.g., for the production of salves.

FIGURE 4.1. Drawing from *Contrafayt Kreuterbuch* by Otto Brunfels, 1532

As the useful and therapeutic properties of local hemp came to be appreciated, Indian hemp, previously unknown in European medicine, was examined in a critical light. The term "Indian Hemp" was first introduced by Georg Eberhard Rumphius who was also the first Westerner to describe the two sexes of the hemp plant. The foreign cannabis plants were treated with caution due to their narcotic properties and supposed harmful effects. In 1777, Johan Friedrich Gmelin from Tübingen wrote, in his book, *Allgemeine Geschichte der Pflanzengifte* (General History of Herbal Poisons):

> The seeds, the bark, the leaves and even more so the juices and buds of this plant have something narcotic; they are the Brug, or Bangue of the Orientals which they use together with honey if they wish to achieve a pleasant type of drunkenness or dizziness. Although I don't doubt that long-term use of this substance could be deadly, as of yet no such example is known to me.[5]

Parallel to academic medicine, Indian hemp also found its way into homeopathic "materia medica." *Cannabis sativa* (indigenous European hemp) was one of the first homeopathic medicines and was mentioned in 1811 in Samuel Hahnemann's *Reine Arzneimittellehre, Erster Theil.* Even today,

classic homeopathy differentiates between the two medicines *Cannabis sativa* and *Cannabis indica*.

CANNABIS IN NINETEENTH-CENTURY WESTERN MEDICINE

At the beginning of the nineteenth century, predominantly native hemp seeds, or occasionally other plant parts, were used pharmaceutically. One of the first extensive descriptions concerning the application of Indian hemp was provided in 1830 by the chemist and botanist Theodor Friedrich Ludwig Nees from Esenbeck:

> Many doctors, even Hahnemann, apply the extract in wine in the case of some nervous complaints where opium or *Hyoscyamus* would otherwise have been used, being more bitter and without heating so much.[10]

Some years earlier, the following text appeared in the then-established *Hufeland-Journal:*

> In a case where help was required quickly, the extract [foliorum?] of cannabis was used in the Berlin Polyclinic against tussis convulsiva [whooping cough] and consequently prescribed in a daily dosage of 4 grains powder mixed with sugar.[3]

In 1839, the Irish doctor William B. O'Shaughnessy published a comprehensive study of Indian hemp[11] titled "On the Preparations of the Indian Hemp, or Gunjah" (see Figure 4.2). Indian hemp consequently gained a foothold in European academic medicine. In the main part of his study, the author described various experiments on humans. Diverse hemp preparations were applied with a high rate of success in the following conditions: rheumatism, rabies, cholera, tetanus, cramps, and delirium tremens. For each symptom, O'Shaughnessy provided case studies and recorded his observations. For the majority of mentioned symptoms, spasmotic phenomena were a central issue. In cannabis he found a good means to provide his patients with relief or even total resolution. In sum he wrote:

> The preceeding cases constitute an abstract of my experience on this subject, and which has led me to the belief that in Hemp the profession has gained an anti-convulsive remedy of the greatest value.[11]

Western medicine reacted promptly to these new findings from India. This is not surprising in light of the fact that, until then, physicians were helpless against infectious illnesses such as rabies, cholera, or tetanus.

FIGURE 4.2. First Page of an Article on Indian Hemp by W. B. O'Shaughnessy, 1839, Calcutta

ON THE PREPARATIONS

OF THE

INDIAN HEMP, OR GUNJAH

(CANNABIS INDICA);

THEIR EFFECTS ON THE ANIMAL SYSTEM IN HEALTH, AND THEIR UTILITY IN THE TREATMENT OF TETANUS AND OTHER CONVULSIVE DISEASES

By W. B. O'SHAUGHNESSY, M.D.,

Assistant-Surgeon, and Professor of Chemistry, &c.

In the Medical College of Calcutta.

Presented October, 1839.

The narcotic effects of Hemp are popularly known in the south of Africa, South America, Turkey, Egypt, Asia Minor, India, and the adjacent territories of the Malays, Burmese, and Siamese. In all these countries Hemp is used in various forms, by the dissipated and depraved, as the ready agent of a pleasing intoxication, In the popular medicine of these nations, we find it extensively employed for a multitude of affections. But in Western Europe, its use either as a stimulant or as a remedy, is equally unknown. With the exception of the trial, as a frolic, of the Egyptian 'Hasheesh,' by a few youths in Marseilles, and of the clinical use of the wine of Hemp by Mahneman, as shewn in a subsequent extract, I have been unable to trace any notice of the employment of this drug in Europe.

Much difference of opinion exists on the question, whether the Hemp so abundant in Europe, even in

WILLIAM B. O'SHAUGHNESSY, 1839

O'Shaughnessy's results brought a ray of hope, particularly because at that time a wave of cholera was raging across Europe and had cost the lives of 18,000 people in Paris alone. A very promising role for cannabis as a medicinal plant had begun.

The French were the first to experiment intensively with the plant. In 1840, Louis Aubert-Roche, a doctor in Egypt, had successfully used hashish against the plague. At more or less the same time, his fellow countryman and friend, the psychiatrist Jaques-Joseph Moreau de Tours had begun to experiment with cannabis. He was convinced that hashish was the preferred cure for mental illness. His book, *Du hachisch et de l'aliénation mentale,* published in 1845, caused a commotion at the time, and is now recognized as the initiation of experimental psychiatry. Inspired by Moreau de Tours and Eugene Soubeiran, the chemist Edmond de Courtive published his doctoral thesis "Haschish" in 1848. He used diverse hashish products to carry out chemical analyses and self-tests whose physical and psychological effects were precisely described.

Due to the promising results demonstrated by the cannabis pioneers, O'Shaughnessy, Aubert-La Roche, and Moreau de Tours, many doctors started employing this new cure in therapy. Initially it was the doctors of the English and French colonial outposts who showed interest in Indian hemp products. The raw materials or substances required were imported to Europe in bulk (mainly from India, but also from Egypt and Algeria).

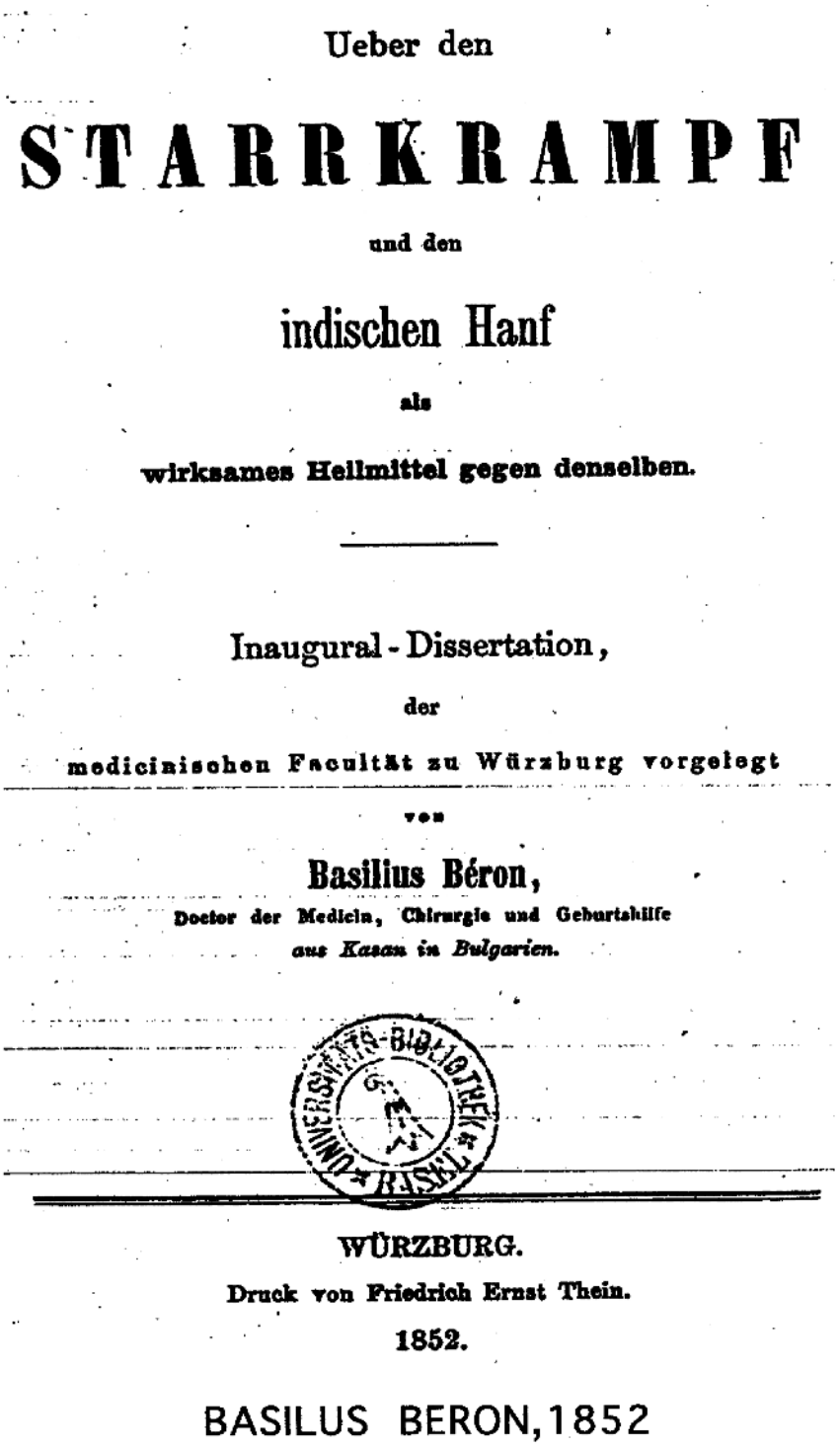
The known indications identified by O'Shaughnessy were initially followed, but the field of therapy with hashish was considerably extended. In particular, initial reports of success in the battle against tetanus led to usage of this new "miracle medicine" by English and French doctors. The Bulgarian doctor Basilus Beron discussed this in his dissertation: "Üeber den Starrkrampf und den indischen Hanf als wirksames Heilmittel gegen denselben" (About Tetanus and the Indian Hemp As Effective Remedy Against It) (see Figure 4.3). The outcome of his work:

> I was so happy – we had tried all known anti-tetanic substances in vain but the Indian hemp showed that the patient assigned to me could be cured completely for which reason Indian hemp must highly be recommended to treat tetanus.[1]

Following Beron, Franz von Kobylanski studied cannabis as a part of his dissertation, specifically its effect as a labor treatment. However, his results were quite sobering. He came to the conclusion that Indian hemp was not a definite means of increasing contractions and could not replace ergot as a proven remedy.

A comprehensive study by Georg Martius appeared in 1856 called "Pharmakognostisch-chemische Studien über den Hanf" (Pharmakognostic-Chemical Studies on Hemp). This raised as much interest as the tests of Carl

FIGURE 4.3. First Page of the Thesis by B. Beron on Tetanus (Starrkrampf) and Indian Hemp, 1852, Würzburg



Ueber den

STARRKRAMPF

und den

indischen Hanf

als

wirksames Heilmittel gegen denselben.

Inaugural-Dissertation,

der

medicinischen Facultät zu Würzburg vorgelegt

von

Basilius Béron,

Doctor der Medicin, Chirurgie und Geburtshilfe

aus Kasan in Bulgarien.

UNIVERSITÄTS-BIBLIOTHEK RASKAU

WÜRZBURG.

Druck von Friedrich Ernst Thein.

1852.

BASILUS BERON,1852

Note: Translation of the title: On tetanus and the Indian hemp as effective remedy against it.

Damian Ritter von Schroff in Vienna who questioned the harmlessness of cannabis products due to their highly differing effects: "the doctor should in any case handle them with the utmost care."[17]

At almost the same time, Ernst Freiherr von Bibra published his renowned work: *Die narkotischen Genussmittel und der Mensch* (The Narcotic Stimulants and the Human Being), in which he dedicated a thirty-page chapter to hashish. Along with the experiences of others he extensively describes his personal trials with hashish. His conclusion:

> The more recent tests and experiences concerning the effects of the hemp plant and its preparations have shown it to be of great advantage.[16]

This promising medicine found its way from Europe to America. In 1860 the Medicinal Commitee of the State of Ohio published a report concerning the application of cannabis products in the United States. Many of the doctors mentioned the known indications from Europe, while others experimented for the first time with new areas of application such as asthma and bronchitis.

THE POSITIVE TREND HOLDS TRUE

The fact that the United States and most European countries adopted Indian hemp into their national pharmacopeias emphasizes that this medicine had been widely accepted. Countless scientific studies of cannabis followed in practically all developed countries.

Research on Indian hemp also advanced in Germany. A comprehensive, often quoted study of this time is that of Bernhard Fronmüller in 1869. He had studied the properties of the hemp plant for some time. His tests with cannabis as a part of his "Klinischen Studien über die schlafmachende Wirkung der narkotischen Arzneimittel" (Clinical Studies on Sleep Inducing Narcotic Medicines) were conducted with exactly 1,000 patients who suffered from sleep disturbances for varied reasons. His results were overall very positive.

1880–1900: THE CLIMAX

This decade can be considered as the climax not only of cannabis research but also of the application of hemp products. In Europe this was mainly due to the Merck company in Darmstadt, Germany, which promoted the availability and usage of cannabis products (see Figure 4.4). Burroughs-Wellcome & Co. in England also produced similar cannabis products. In the United States the Bristol-Meyers Squibb company in New York, Parke-

FIGURE 4.4. Advertisement by the Company E. Merck in Darmstadt (Germany), Around 1885

Davis and Company in Detroit, and Eli Lilly and Company in Indianapolis also played leading roles. High-quality raw materials and finished products were consequently available to the public.

At the turn of the century, cannabis had attained a prominent position in Europe and the United States as a treatment for pain (especially migraines and menstrual cramps), whooping cough, asthma, and as a soporific/sedative. In addition, Indian hemp was often found as an ingredient in remedies for corns. The following complaints were treated with cannabis on a smaller scale: stomach pains and gastrointestinal disorders, depression, diarrhea, anorexia, itching, bleeding in the womb, Grave's disease, and malaria.

Many doctors who had studied the medicinal uses of cannabis over a period of many years categorized it as a valuable substance. Others disregarded it or even considered it dangerous. However, both parties agree that the effects of cannabis products were variable, and occasionally uncertain.

Also at the turn of the century, many different pharmaceutical preparations could be found on the market, and were prescribed by doctors and stocked by chemists. The initial mass production of cannabis preparations occurred in the middle of the nineteenth century. The brothers T. and S. Smith in Edinburgh marketed one of the first products, Cannabin. Of the cannabis medicines on the market at the turn of the century, most were designed to be taken orally, while about a third were to be applied externally and a few were employed by inhalation. Asthma cigarettes containing cannabis or other ingredients were particularly favored at this time. Although single ingredient preparations dominated the market in the nineteenth century, over the course of time, more and more combination products became available. After the turn of the century, pure cannabis products had already become more scarce, usually in the form of pharmacy formulas. Probably the most popular cannabis medicine of all was Bromidia, a sleeping pill which also contained potassium bromide, chloral hydrate and *Hyoscyamus niger* (henbane). This was introduced in 1886 and was still prescribed in 1959 in Switzerland, but by that time it was classified as a narcotic.

The "Indian Hemp Drugs Commission Report" written in 1894 made an extremely important scientific contribution to cannabis research. This English survey, carried out in the colony of India, mainly concerned the investigation of production of drugs from cannabis, attendant trade and business, and their effects on the population as a whole. Furthermore, the authorities sought to clarify whether or not a complete ban of cannabis products would be justified. For this purpose, a committee of experts was formed. Their report was designed to comprehensively examine the issue of cannabis in India as a medicine and as a recreational substance at the end of the nineteenth century. Essentially, the committee came to the following conclusion: "Due to the effects of hemp drugs, it does not seem necessary to the committee to forbid growing of the hemp plant, the production of hemp drugs and the sale thereof."[7]

CANNABIS AS A MEDICINE IN THE TWENTIETH CENTURY

At the beginning of the twentieth century, many chemically oriented studies of cannabis appeared, in line with the trend of that era. Science endeavored to uncover the secret of the "active principle" of this plant.

Switzerland took an active role in the research of cannabis at the beginning of the twentieth century. Even though Indian hemp was recognized and appreciated as a medicinal substance in Switzerland, scientific research had up until then been left to other countries. Last but not least, the blooming chemical industry in Basel, Switzerland, began to show an interest in cannabis. Hoffmann-La Roche & Co. patented a process in 1914 which extracted the pharmacologically effective ingredients of *Cannabis indica*. It was hoped that the medicinal substances obtained through this process could be used therapeutically. However, no Hoffmann-La Roche cannabis product ever came to market.

In particular, the Pharmacological Institution of the Bern University developed into the most renowned cannabis research laboratory in Switzerland. Under the direction of the pharmacologist Emil Bürgi, some thirty dissertations on the subject of cannabis appeared over three decades. The majority of these studies investigated combining cannabis with other medicinal substances. The authors almost always achieved a positive outcome in the sense that an increase in efficacy was observed.

AN ERA COMES TO AN END

Despite initial popularity, cannabis substances almost completely disappeared around the middle of the twentieth century. The main reasons for the disappearance of hashish medicines are listed as follows.

Pharmaceutical Development

Specific substitute pharmaceuticals were introduced even before the beginning of the twentieth century that treated all the main indications for which cannabis had been utilized. For the treatment of infectious diseases (cholera, tetanus, etc.), vaccines were developed that offered protection against infection. Other bacterial diseases such as gonorrhea which were frequently treated annabis could later be treated by chemotherapy (salvarsan was introduced into therapy by Paul Ehrlich in 1910). As a narcotic and a sedative, cannabis was rivaled by substances such as chloral hydrate, paraldehyde, sulfonal, barbiturates, and bromural. Contrary to the many opiates, cannabis substances as analgesics were soon replaced by synthetic substances. Antipyrine and aspirin were rapidly of great significance soon after their introduction.

Pharmaceutical Instability

It has already been mentioned that the varying efficacy of cannabis substances was problematic. Many different factors, such as the origin, age, storage and preparation of the drug were directly responsible for the variations in clinical results with these medicines. In contrast to the alkaloid drugs codeine and morphine, which are derived from opium, isolation of the active substances from cannabis was not achieved until the 1960s. There remained the issue and difficulty of standardization.

Economic Aspects

Due to restrictions in the countries of production (especially India) and the disruptions of the World Wars, it became more and more difficult to import high-quality cannabis to Europe. The law of supply and demand was also valid for cannabis as a drug, which meant that the price of the raw product and the prepared substances rose rapidly.

Legal Restrictions

National and international laws became increasingly restrictive and thus impeded the application of cannabis medicines. Sooner or later cannabis substances were addressed by national narcotic acts, which considerably hindered their practical application. Finally, a general ban made it impossible to continue applying cannabis medicinally.

CONCLUSION

When cannabis medicines disappeared half a century ago, this was not perceived in most circles as a critical restriction of the therapeutic arsenal.

However, the situation today is somewhat different. Modern cannabis research and traditional usages along with modern anecdotal reports indicate that cannabis can be the drug of choice for certain patients and conditions. The future will demonstrate whether cannabis in medicinal context must forever remain a subject of the past. Hope remains that circumstances will not stand in the way of a possible enrichment of the world of therapy.

REFERENCES

1. Beron B. Ueber den Starrkrampf und den indischen Hanf. MD Dissertation, University of Würzburg, 1852, pp. 5, 48.

2. De Fouquet M. *Sehr nützliches Artzney-Buch, aus dem französischen ins teutsche übersetzt bey Johann Jacob Winklrn*. Dresden, 1708, p. 160.

3. Dierbach JH. *Die neusten Entdeckungen in der Materia medica*. Heidelberg and Leipzig, 1828, p. 420.

4. Dioskurides aus Anazarbos. *Arzneimittellehre in fünf Büchern*. Translated by J. Berendes, reprint of the edition of 1902, Wiesbaden: Ferdinand Ehnke, 1970, p. 359.

5. Gmelin JF. *Allgemeine Geschichte der Pflanzengifte*. Nürnberg, 1777, p. 402.

6. Homerus: *Odysee*. Verdeutscht von Thassilo von Scheffer. New edition. Leipzig: Dietrich, 1938, p. 55.

7. Leonhardt RW. *Haschisch-Report, Dokumente und Fakten zur Beurteilung eines sogenannten Rauschgiftes*. München, 1970, p. 86.

8. Matthioli PA. *Kreutterbuch des hochgelehrten und weitberühmten Herrn D. Petri Andrea Matthioli. Gemehret und verfertigt durch Ioachimum Camerarium.* Frankfurt, 1626 (Facsimile).

9. *Medizinisches Lexikon. Mit einer Vorrede von Albrecht von Haller*. Ulm/Frankfurt/Leipzig, 1755, p. 290.

10. Nees v. Esenbeck TFL, Ebermaier CH. *Handbuch der medicinisch-pharmaceutischen Botanik*. Düsseldorf, Erster Theil, 1830, pp. 338-339.

11. O'Shaugnessy WB. On the preparations of the Indian hemp, or Gunjah, *Transactions of the Medical and Physical Society of Bengal* (1838-1840), 421-461. Reprint in: Mikuriya TH, ed. *Marijuana: Medical papers 1839-1972*. Oakland, CA: Medi-Comp Press, 1973, p. 29.

12. Reier H. *Die altdeutschen Heilpflanzen, ihre Namen und Anwendungen in den literarischen Ueberlieferungen des 8.-14. Jahrhunderts*. 1. Band: A bis H, Kiel: Selbstverlag, 1982, p. 204.

13. Schleiden, zitiert nach: Tschirch A. *Handbuch der Pharmakognosie*. Erste Abteilung. Leipzig: Verlag von Chr. Herm. Tauchnitz, 1909, p. 3.

14. Schröder DJ. *Vollständiger Arzney-Schatz, in fünff Bücher eingetheilt*. Frankfurt/Leipzig, 1709, p. 902.

15. Tode JC. *Erleichterte Kenntniss und Heilung des Trippers*. Kopenhagen/Leipzig, 1790, pp. 246-249.

16. Von Bibra E. *Die narkotischen Genussmittel und der Mensch.* Nürnberg, 1855, p. 290.

17. Von Schroff KD. *Fall einer Vergiftung mit Haschisch.* N Rep Pharm, Band VII, München, 1858, p. 112.

PART II: PHARMACOLOGY AND PHARMACOKINETICS

Chapter 5

Effects of Cannabis and the Cannabinoids

Franjo Grotenhermen

> [After one hour] quite suddenly there is developed an indescribable feeling of exaltation and of grandeur. The words "fine," "superfine," and "grand" come into my mind as being applicable to the feeling. This indescribable feeling is purely subjective. . . . The idea of oneness with all nature and with the entire universe seems to take hold. There is no material body or personality. . . . There is a marvelous color imagery, blue, purples and gold predominating with most delicate shading effects. . . . Evidently sleep gradually set in and continued undisturbed until the usual rising time. No special sensation on rising. Feeling, if anything, more than usually refreshed. All of the sensations recorded above have completely vanished. The recollections of the experiences are however clear and vivid.

This description of an intentional overdose of a physician named Schneider from 1938[24] gives an impression of the pharmacological effects that have made cannabis one of the most popular recreational drugs of the present time, alongside alcohol, tobacco, and caffeine. In addition, cannabis is capable of producing a multitude of physical effects (see Table 5.1), through specific receptor mechanisms (see Chapter 7) (see Figures 5.1 and 5.2).

The cannabinoid signaling system is teleologically millions of years old. It has been observed in mammals, fishes, and invertebrates down to very primitive organisms, such as the hydra.[4] Its activation through herbal, synthetic, and endogenous cannabinoids causes numerous actions, which have been extensively reviewed[1,6,11,11-15,19,25] (see Figure 5.3). In recent years, additional nonreceptor-mediated effects have come into focus as well (see Chapters 9, 33, 35, and 36).

Most of the constituents of the hemp plant, among them terpenoids, hydrocarbons, amino acids, fatty acids, sugars, etc. (see Chapter 3), are ubiquitous in other herbal and animal organisms. Most are of minor pharmacological and toxicological relevance, but some noncannabinoid compounds may modulate the effects of the cannabinoid components (see Chapter 37).[5]

TABLE 5.1. Effects of Cannabis and THC

The following dose-dependent effects were observed in clinical studies, in vivo, or in vitro, respectively:

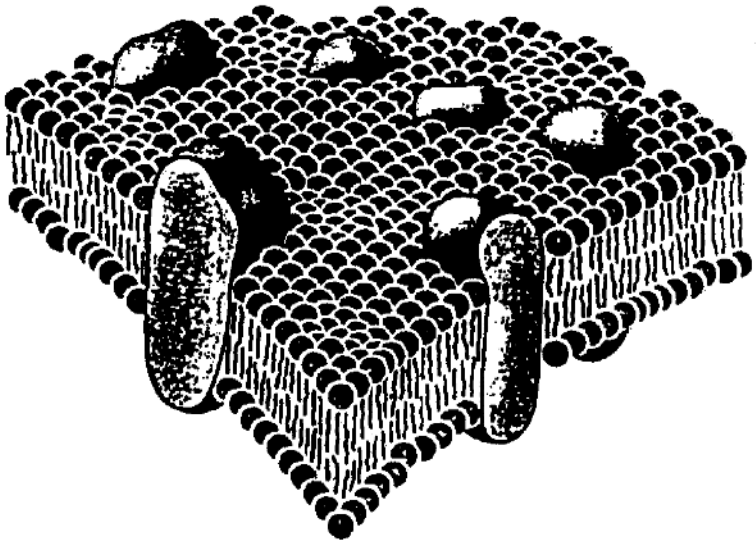
- *Psyche and perception:* fatigue, euphoria, enhanced well-being, dysphoria, anxiety, reduction of anxiety, depersonalization, increased sensory perception, heightened sexual experience, hallucinations, alteration of time perception, psychotic states.
- *Cognition and psychomotoric performance:* fragmented thinking, enhanced creativity, disturbed memory, unsteady gait, ataxia, slurred speech, deterioration or amelioration of motor coordination.
- *Nervous system:* analgesia, muscle relaxation, appetite stimulation, vomiting, antiemetic effects, neuroprotection in ischemia and hypoxia.
- *Body temperature:* decrease of body temperature.
- *Cardiovascular system:* tachycardia, enhanced heart activity and increase in oxygen demand, vasodilation, orthostatic hypotension, hypertension (in horizontal position), inhibition of platelet aggregation.
- *Eye:* injected (reddened) conjunctivae, reduced tear flow, decrease of intraocular pressure.
- *Respiratory system:* bronchodilation, hyposalivation, and dry mouth.
- *Gastrointestinal tract:* reduced bowel movements and delayed gastric emptying.
- *Hormonal system:* influence on LH, FSH, testosterone, prolactin, somatotropin, TSH, glucose metabolism, reduced sperm count and sperm motility, disturbed menstrual cycle and suppressed ovulation.
- *Immune system:* impairment of cell-mediated and humoral immunity, anti-inflammatory, and immune-stimulating effects.
- *Fetal development:* malformations, growth retardation, impairment to fetal and postnatal cerebral development, impairment of cognitive functions.
- *Genetic material and cancer:* antineoplastic activity, inhibition of synthesis of DNA, RNA, and proteins.

Delta-9-THC is the pharmacologically and toxicologically most relevant constituent of the hemp plant, responsible for most of the effects of natural cannabis preparations. The pharmacological action of Δ^9-THC is stereoselective, and the natural (–)-*trans* isomer is 6 to 100 fold more potent than the (+)-*trans* isomer depending on the assay.

EFFECTS ON PSYCHE AND BEHAVIOR

In many species the behavioral actions of low doses of Δ^9-THC are characterized by a unique mixture of depressant and stimulant effects in the cen-

FIGURE 5.1. The Cell Membrane with the Lipids Arranged in a Bilayer and Proteins (Such As Receptors) Penetrating the Membrane



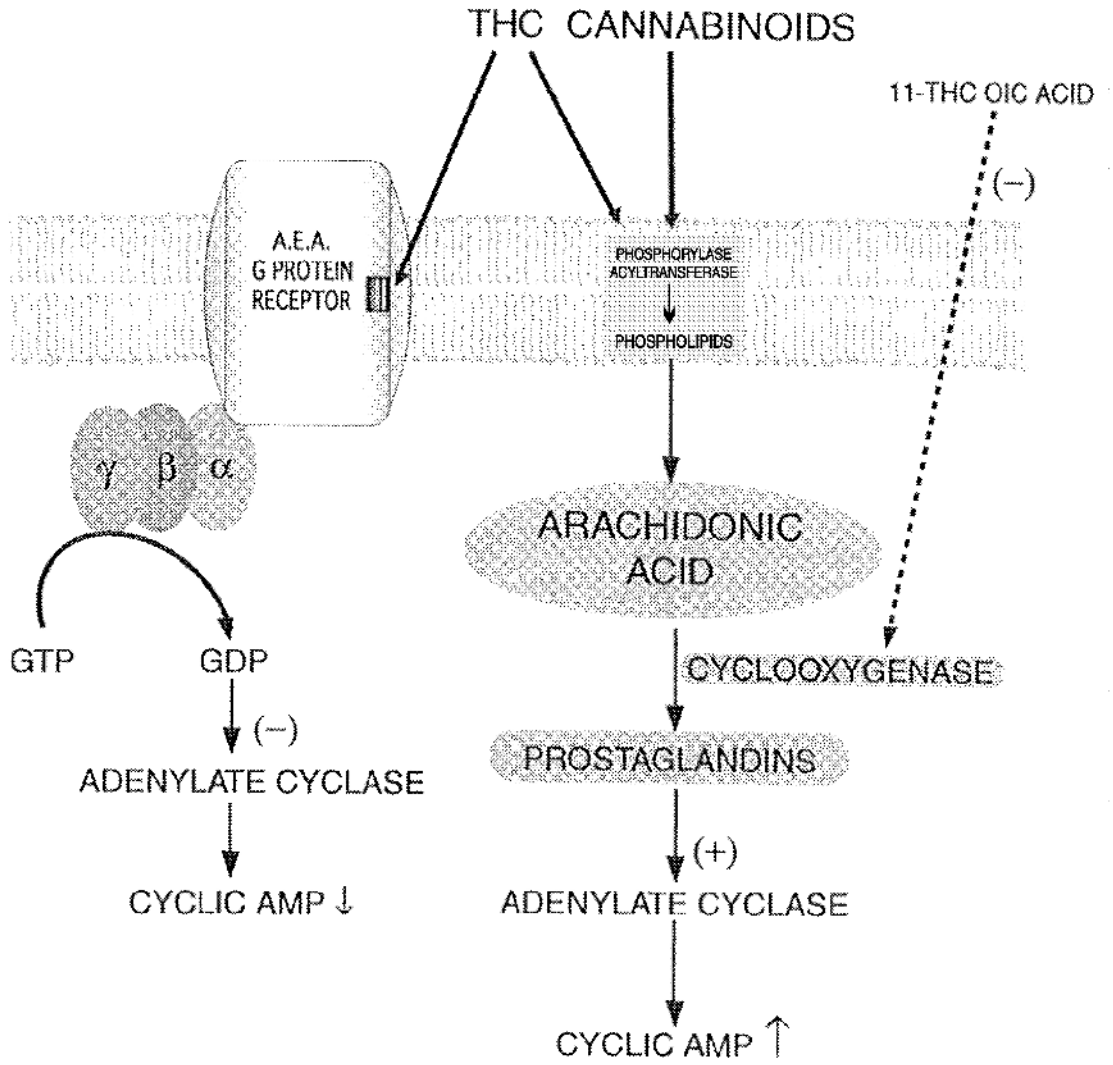
Source: Stryer L. *Biochemistry,* Fourth Edition. New York: W. H. Freeman and Company, 1995, p. 278. Reprinted with permission. American Association for the Advancement of Science.

tral nervous system (CNS). The so-called "popcorn" effect in mice is characteristic: A group of mice present in a sedated state until a stimulus causes one of them to jump (hyperreflexia). This mouse then falls on another, causing that one to jump as well. This process continues until all the mice are sedated again, when a later phase of hyperreflexive jumping may be initiated. Following the application of psychotropic cannabinoids to other animals, similar states obtain, characterized by a combination of sedation/catalepsy and hyperreflexia.

Delta-9-THC and some synthetic cannabinoid agonists impair learning and memory in animals. Tolerance develops to these effects. In one experiment, rhesus monkeys were given cannabis for one year. Task performance was impaired for over a week after cessation of use and normalized within three weeks, without signs of residual behavioral effects.[1]

The most conspicuous psychological effects of THC in humans have been divided into four groups by Perez-Reyes: affective (euphoria and easy laughter), sensory (increased perception of external stimuli and of the person's own body), somatic (feeling of the body floating or sinking in the bed), and cognitive (distortion of time perception, memory lapses, difficulty in concentration). The quality of these psychological effects in healthy individuals did not differ according to the route of application (oral, inhalative,

FIGURE 5.2. Effects of THC and Cannabinoids on Phospholipid and Arachidonic Acid Biochemical Pathways



Source: Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and Medicine.* Totowa, NJ: Humana Press, 1999, p. 795. Reprinted with permission.

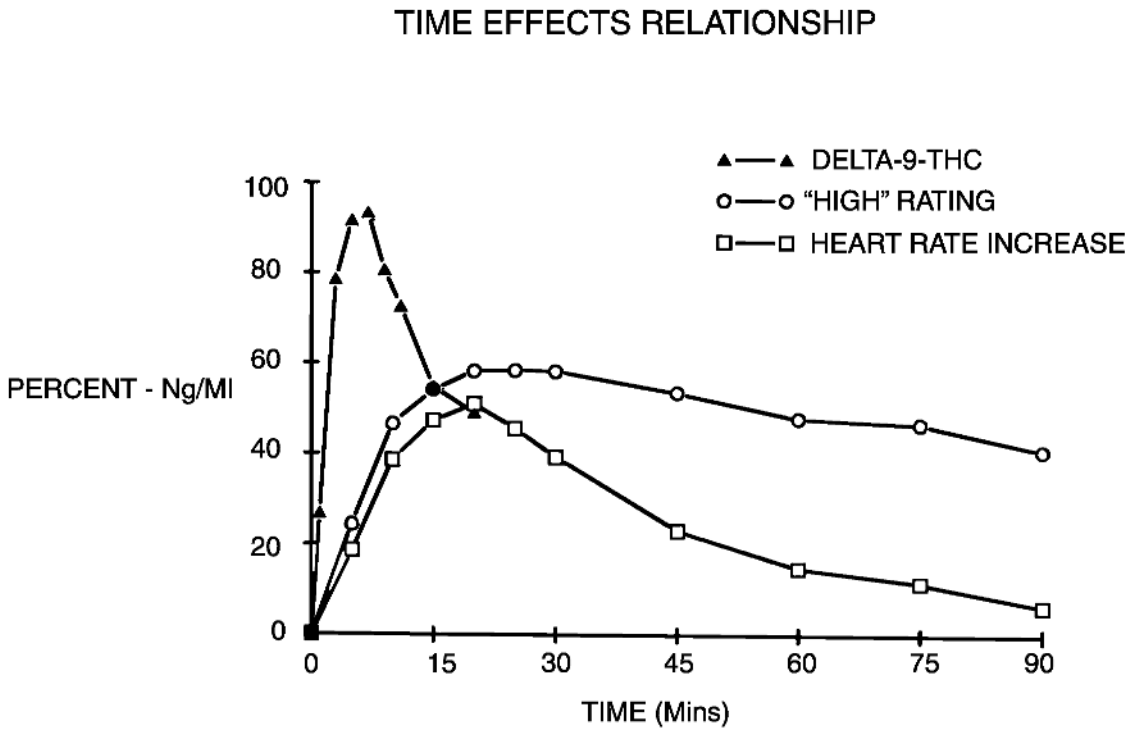
Note: THC is bound to a G protein receptor that influences adenylate cyclase dependent processes.

intravenous).[19] Many physical effects are achieved below the threshold of psychological effects.

CENTRAL NERVOUS SYSTEM AND NEUROCHEMISTRY

THC increases the metabolic rate in the brains of animals and humans.[1] Most cannabinoid effects (analgesia, appetite enhancement, muscle relax-

FIGURE 5.3. Time Effects Relationship Following Smoked Marijuana



Source: Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and Medicine.* Totowa, NJ: Humana Press, 1999, p. 251. Reprinted with permission.

Note: THC plasma concentration reaches its maximum after approximately five minutes and is already decreasing when psychic effects ("high") and heart rate reach their maximum after 15 to 30 minutes.

ation, hormonal actions, etc.) are mediated by central cannabinoid receptors. Their distribution (see Chapter 7) reflects many of the medicinal benefits and side effects described in this volume. Neuroprotective properties of different cannabinoids (Δ^9-THC, CBD, dexanabinol) in ischemia and hypoxia are examples of some known receptor-independent actions of cannabinoids (see Chapters 9 and 36).

Cannabinoids interact with a multitude of neurotransmitters and neuromodulators (see Chapter 7). Among them are acetylcholine, dopamine, γ-aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptids. A number of pharmacological effects can be explained (at least in part) on the basis of such interactions. For example, tachycardia and hyposalivation with dry mouth are mediated by the effects of THC on release and turnover of acetylcholine.[7] Antiemetic properties may be due to

interactions with serotonin (see Chapter 14). Catalepsy and hypomotility could be mediated by acetylcholine, GABA, and prostaglandins. Therapeutic effects in movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutamergic, and dopaminergic transmitters systems (see Chapters 17 and 18).

CIRCULATORY SYSTEM

THC can induce tachycardia and increase cardiac output with increased cardiac labor and oxygen demand. It can also produce peripheral vasodilation, orthostatic hypotension and reduced platelet aggregation. The tachycardic effect of THC is presumably based on vagal inhibition and can be attenuated by beta-blockers. Due to tolerance to these effects, chronic use can lead to bradycardia. CBD has little effect on heart rate and increases coronary flow. CBN decreases heart rate without affecting coronary blood flow.

One of the most important physiological functions of endocannabinoids might be the regulation of blood pressure and tonus of blood vessels. Possible mechanisms comprise a cannabinoid-receptor mediated inhibition of norepinephrine release from sympathetic nerves and/or a direct vasodilation through activation of endothelial CB-receptors.[23] Endocannabinoids seem to be produced by the vascular endothelium, circulating macrophages and platelets.[23]

OTHER ORGAN SYSTEMS AND EFFECTS

Antibacterial and antiviral actions. Antibacterial actions have been demonstrated for CBD, CBG, and Δ^9-THC. Incubation with Δ^9-THC reduces the infectious potency of herpes simplex viruses.

Eye. Vasodilation in the eye is observed as conjunctival injection after THC exposure. Other effects are reduction of tear flow with possible increased susceptibility to infectious diseases (keratitis, conjunctivitis). THC and some other cannabinoids decrease intraocular pressure. The evidence of cannabinoid receptors at different sites (anterior eye, retina, corneal epithelium) suggests that cannabinoids influence different physiological functions in the human eye (see Chapter 19).

Musculoskeletal. THC relaxes muscles, and has hypokinetic and anticonvulsant effects. Higher doses may reduce strength and impair coordination, leading to possible falls.

Blood. Cannabis components inhibit platelet aggregation, with decreasing potency as follows: CBG, CBD, olivetol, THC, and CBN.

Hormonal system and fertility. Marijuana interacts with the hypothalamic-pituitary adrenal axis influencing numerous hormonal processes (see

Chapter 26). Tolerance develops to these effects, however, and even heavy cannabis users demonstrate normal hormone levels.

Withdrawal. THC reduces naloxone induced withdrawal in morphine-dependent rats.

Epilepsy: Anticonvulsant effects have been described for psychotropic and nonpsychotropic cannabinoids (Δ^9-THC, CBD, CBN, 11-OH-Δ^9-THC, and Δ^8-THC).

Genetic and cell metabolism. THC can inhibit DNA, RNA, and proteins synthesis, and can influence the cell cycle. Very high doses are required to produce this effect in vitro. Cannabinoid agonists, among them THC, applied directly at the tumor site showed antineoplastic activity against malignant gliomas in rats.[9]

Immune system. Animal and cell experiments have demonstrated that THC exerts complex effects on cellular and humoral immunity (see Chapters 10, 21, and 25). It is not clear, whether and to what extent these effects are of clinical relevance in humans with respect to beneficial (inflammation, allergies, autoimmune processes) and undesirable effects (decreased resistance towards pathogens and carcinogens).

Body temperature. Δ^9-THC decreases body temperature, to a greater degree in hyperthermic than in euthermic animals. High doses are required.

Sperm. Endocannabinoids may possibly play a role in the regulation of human sperm function, binding to CB receptors, and possibly to distinct CB receptor subtypes. In animal studies high doses of cannabinoids inhibited the acrosome reaction.[2]

Migraine. Δ^9-THC inhibits serotonin release from platelets taken from patients during a migraine attack, while no such effect was observed during disease-free intervals.

Respiration and lung. THC exerts an atropine-like effect on salivary secretion resulting in dry mouth. It also causes bronchodilation.

Sleep. Δ^9-THC induces sleep. As with conventional hypnotics it decreases REM sleep time dose-dependently, without a pronounced REM rebound observed with cessation of other hypnotics. A direct effect stimulation of melatonin secretion by Δ^9-THC may play a role.[16]

Neurovegetative. Inhibition of the parasympathetic and activation of the sympathetic tone seem to play a role in some actions of cannabis (increase of heart rate, bronchodilation).

Digestive tract. Anandamide induces overeating in rats through a CB_1 receptor mediated mechanism (see Chapter 13). Cannabinoid agonists inhibit the activation of 5-HT_3 receptors, a possible mechanism of their anti-emetic effect (see Chapter 14). Cannabinoid agonists inhibit gastrointestinal motility and gastric emptying in rats. In a recent double-blind study in healthy individuals an oral dose of Δ^9-THC of 10 mg/m^2 caused a significant delay in gastric emptying compared to placebo.[17] In addition, CB agonists inhibited

pentagastrin-induced gastric acid secretion in the rat, presumably by a CB receptor dependent process.[3]

TOLERANCE

Tolerance develops to many THC effects (see Chapter 23).[21] Among them are behavioral actions, tachycardia, hypotension, effects on sex hormones, stimulation of prostaglandin E_2 production, and inhibition of adenyl cyclase activity. Tolerance does not develop to all effects nor with the same speed and intensity. Tolerance to the tachycardic effects occurs within a few days of continued usage. Administration of THC for a period of five days did not result in tolerance to the stimulating effects on adrenocorticotropin hormone (ACTH) secretion.

O'Shaughnessy (1839) reported development of tolerance in connection with the medical use of a tincture of "Indian hemp." Two out of three cases of rheumatism showed good improvement, while the third patient did not respond to the therapy. Ultimately the latter admitted being "habituated to the use of gunjah (cannabis) in the pipe" (see Chapter 4).

Tolerance to cannabinoid effects may occur due to pharmacodynamic changes (downregulation and internalization of receptors), or to a lesser extent due to pharmacokinetic changes (absorption, metabolism). Downregulation of cannabinoid receptors differs in distinct brain areas and corresponds to the resulting effects. Application of THC over a period of five days decreased specific receptor binding in different receptor sites of the brain ranging from 20 to 60 percent.[22] Since tolerance does not develop to the actions of the acid metabolite THC-COOH (THC-11-oic-acid) some differences in tolerance for different effects may be due to additional nonreceptor-mediated effects (see Chapter 35).

DRUG INTERACTIONS

Interactions with other drugs may depend on activity on similar effector systems or metabolic interactions[18, 20] (see Chapter 31). Since cannabinoids are strongly bound to proteins, interactions with other protein-bound drugs may also occur.

CANNABINOID INTERACTIONS

CBD decreased Δ^9-THC actions on heart rate, respiration, and body temperature in rabbits, but enhanced its analgesic properties in rats. Cannabichromene has a low analgesic effect in mice, but increased the analgesic action of THC. These inhibiting or reinforcing interactions may be in part

responsible for the observation that, in clinical usage, pure THC may act more strongly than marijuana of the same THC content with respect to hypothermic effects, or more weakly as a cataleptic (see Chapter 37).

ACTIONS OF OTHER CANNABINOIDS

Delta-8-Tetrahydrocannabinol (Δ^8-THC) is a positional isomer of Δ^9-THC with a similar pharmacological profile and slightly lower potency. Whether it is a natural cannabinoid or an artifact of analysis is unclear (see Chapter 3). The most important psychotropic metabolite of Δ^9-THC, *11-OH-Δ^9-tetrahydrocannabinol,* has a similar spectrum of actions as the parent molecule (see Chapter 6). Behavioral changes in apes following the administration of 11-hydroxy-Δ^9-THC occurred faster than with Δ^9-THC which were three times stronger, and had a shorter duration. After intravenous application in humans, 11-OH-Δ^9-THC and Δ^8-THC produced effects similar to Δ^9-THC. With regard to psychological effects, 11-OH-Δ^9-THC and Δ^9-THC were equipotent, while Δ^8-THC was 50 percent as potent.[19] Following intravenous application (0.2 mg/min), the mean reduction in intraocular pressure was 33 percent with Δ^9-THC, 34 percent with 11-OH-THC, and 37 percent with Δ^8-THC. The latter drug thus possessed the best therapeutic index for this indication.

The most important nonpsychotropic metabolite of Δ^9-THC is *11-nor-9-carboxy-THC* (THC-COOH) (see Chapter 6). For a long time it was regarded as pharmacologically inactive. Recent research has demonstrated, however, that it possesses anti-inflammatory and analgesic properties possibly contributing to the THC effect to a significant extent (see Chapter 35). On the other hand, THC-COOH-Δ^9 antagonizes some effects of the parent drug through an unknown mechanism (for example, the cataleptic effect in mice) (see Chapter 35). Due to the comparatively long half-life of the metabolite, its action may influence the overall effect of THC or cannabis in chronic usage.

Cannabinol (CBN) is a very weakly psychotropic cannabinoid, whose effect is only measurable with intravenous application. CBN has shown anticonvulsant effects, decreases in heart rate, a decrease in intestinal motility, and an inhibition of platelet aggregation.

Cannabidiol (CBD), cannabigerol (CBG), and *cannabichromene (CBC)* are the main nonpsychotropic cannabinoids. The pharmacological actions of cannabidiol have been most investigated. Sedating, hypnotic, antiepileptic, antidystonic, and immune modulating effects were observed, and it reduced intraocular pressure.[10] It antagonizes the psychotropic effects of THC. Anxiolytic antipsychotic properties might prove useful in psychiatry (see Chapter 33). CBG and CBC showed sedative effects, as well. CBG has been observed to decrease intraocular pressure and has antibiotic properties.

Anandamide, an endocannabinoid, produces pharmacological effects similar to those of Δ^9-THC, among them analgesia, catalepsy, hypomotility, hypothermia, and activation of the hypothalamic-pituitary adrenal axis. Depending on the investigated effect, anandamide was 4 to 20 times less potent than THC and showed a marked shorter time of action. However, there are apparently some significant differences with THC. Under certain circumstances, anandamide acts as a partial agonist at the CB_1 receptor, while THC is a full agonist.[8] Very low doses of anandamide antagonized the actions of THC. The authors assumed that low doses of anandamide activated stimulating G_s protein pathways and not inhibiting G_i proteins (see Chapter 7), or caused an allosteric modulation of the cannabinoid receptor.[8]

REFERENCES

1. Adams IB, Martin BR. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 1996;91(11):1585-1614.

2. Chang MC, Berkery D, Schuel R, Laychock SG, Zimmerman AM, Zimmerman S, Schuel H. Evidence for a cannabinoid receptor in sea urchin sperm and its role in blockade of the acrosome reaction. *Molecular Reproduction and Development* 1993;36(4):507-516.

3. Coruzzi G, Adami M, Coppelli G, Frati P, Soldani G. Inhibitory effect of the cannabinoid receptor agonist WIN 55,212-2 on pentagastrin-induced gastric acid secretion in the anaesthetized rat. *Naunyn-Schmiedebergs Archives of Pharmacology* 1999;360(6):715-718.

4. De Petrocellis L, Melck D, Bisogno T, Milone A, Di Marzo V. Finding of the endocannabinoid signalling system in Hydra, a very primitive organism: Possible role in the feeding response. *Neuroscience* 1999;92(1):377-387.

5. Deutsch HM, Hodges LC, Zalkow LH. Prostaglandin involvement in the responses of the rabbit eye to water-soluble marihuana-derived material. *Current Eye Research* 1987;6(2):337-344.

6. Dewey WL. Cannabinoid pharmacology. *Pharmacological Reviews* 1986; 38(2):151-178.

7. Domino EF. Cannabinoids and the cholinergic system. In Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999, pp. 223-226.

8. Fride E, Barg J, Levy R, Saya D, Heldman E, Mechoulam R, Vogel Z. Low doses of anandamides inhibit pharmacological effects of delta 9-tetrahydrocannabinol. *Journal of Pharmacology and Experimental Therapeutics* 1995;272(2):699-707.

9. Galve-Roperph I, Sanchez C, Cortesz ML, Gomez del Pulgar T, Izquierdo M, Guzman M. Antitumoral action of cannabinoids: Involvement of sustained ceramide accumulation and ERK activation. *Nature Medicine* 2000;6(3):313-319.

10. Grotenhermen F. Die Wirkungen von Cannabis und THC. *Forschende Komplementärmedizin, [Research in Complementary Medicine]* 1999;6(Suppl 3):7-11.

11. Grotenhermen F, Karus M. Industrial hemp is not marijuana. Comment on the drug potential of fibre Cannabis. *Journal of the International Hemp Association* 1999;5(2):96-101.

12. Grotenhermen F, Karus M. Marihuana. Kurzstudie zum Stand der rechtlichen Situation in Deutschland und zum Stand der medizinischen Forschung. In Grinspoon L, Bakalar JB, eds. *Marihuana, die verbotene Medizin*. Frankfurt: Zweitausendeins, 1994 (1st edition), 1998 (10th edition).

13. Hall W, Solowij N, Lemon J. *The health and psychological consequences of cannabis use*. Canberra: Commonwealth Department of Human Services and Health, Monograph Series No. 25, 1994.

14. Hollister LE. Health aspects of cannabis. *Pharmacological Reviews* 1986; 38(1):1-20.

15. Joy JE, Watson SJ, Benson JA, eds. *Marijuana and medicine: Assessing the science base*. Washington DC: Institute of Medicine, National Academy Press, 1999.

16. Lissoni P, Resentini M, Mauri R, Esposti D, Esposti G, Rossi D, Legname G, Fraschini F. Effects of tetrahydrocannabinol on melatonin secretion in man. *Hormone and Metabolic Research* 1986;18(1):77-78.

17. McCallum RW, Soykan I, Sridhar KR, Ricci DA, Lange RC, Plankey MW. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: A double-blind, randomized study. *Alimentary Pharmacology and Therapeutics* 1999;13(1):77-80.

18. Perez-Reyes M, Burstein SH, White WR, McDonald SA, Hicks RE. Antagonism of marihuana effects by indomethacin in humans. *Life Sciences* 1991;48(6):507-515.

19. Perez-Reyes M. The psychologic and physiologic effects of active cannabinoids. In Nahas G, Sutin KM, Harvey DJ, Agurell S. *Marihuana and Medicine*. Totowa, NJ: Humana Press, 1999, pp. 245-252.

20. Pryor GT, Husain S, Mitoma C. Acute and subacute interactions between delta-9-tetrahydrocannabinol and other drugs in the rat. *Annals of the New York Academy of Sciences* 1976;281:171-189.

21. Romero J, Berrendero F, Manzanares J, Perez A, Corchero J, Fuentes JA, Fernandez-Ruiz JJ, Ramos JA. Time-course of the cannabinoid receptor down-regulation in the adult rat brain caused by repeated exposure to Δ^9–tetrahydrocannabinol. *Synapse* 1998;30(3):298-308.

22. Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ. Effects of chronic exposure to delta-9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Brain Research. Molecular Brain Research* 1997;46(1-2):100-108.

23. Wagner JA, Varga K, Kunos G. Cardiovascular actions of cannabinoids and their generation during shock. *Journal of Molecular Medicine* 1998;76(12):824-836.

24. Walton RP. Description of the hashish experience. In *Marihuana: America's new drug problem*. Philadelphia: JB Lippincott, 1938.

25. World Health Organization: *Cannabis: A health perspective and research agenda*. Geneva: Division of Mental Health and Substance Abuse, WHO, 1997.

Chapter 6

Pharmacokinetics

Rudolf Brenneisen

GENERAL

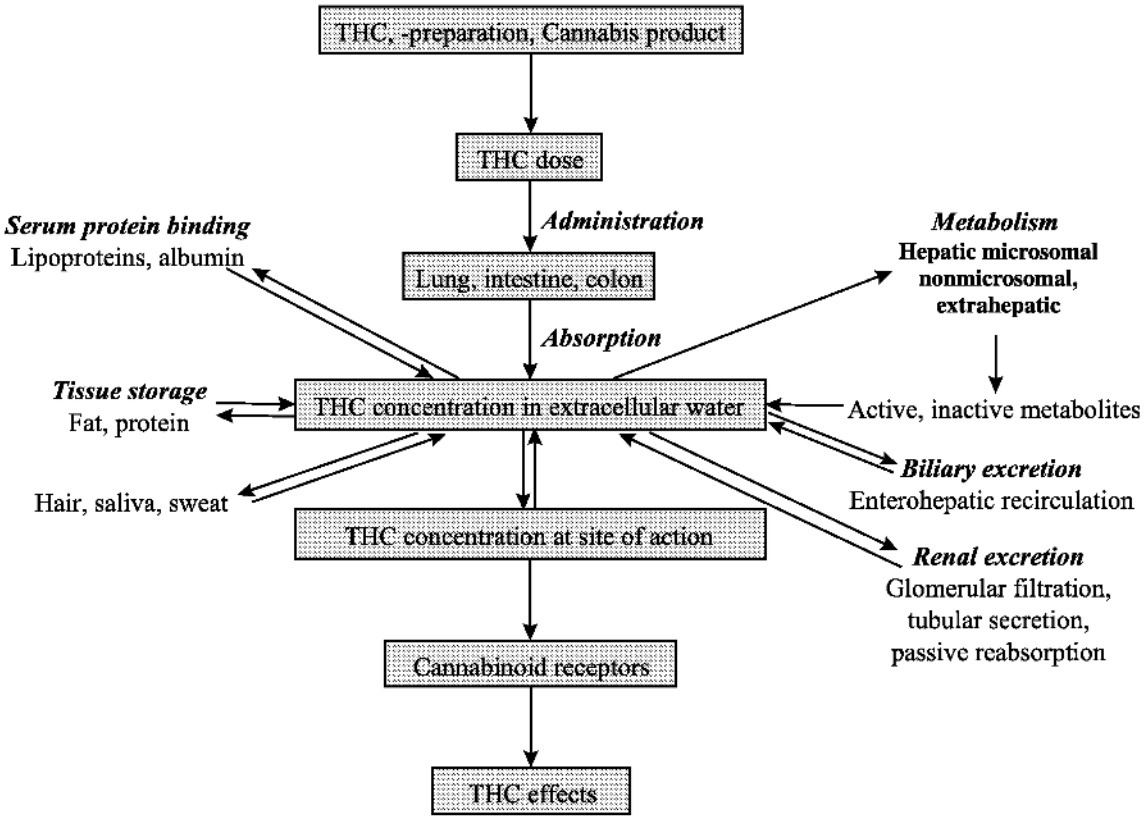
The pharmacokinetically best studied substance among the natural cannabinoids is Δ^9-tetrahydrocannabinol (THC). The kinetic profiles of cannabidiol (CBD), the other major natural cannabinoid, and cannabinol (CBN), the THC decomposition product formed by oxidation, are very similar to that of THC. No significant differences in the pharmacokinetics of women and men have been found. The complexity of the pharmacokinetic properties of THC influencing its pharmacodynamic characteristics is shown in Figure 6.1. For supporting literature, refer to the reviews of Harvey,[2] Huestis,[3] and Kleiber and Kovar.[4]

ABSORPTION AND BIOAVAILABILITY

A very rapid absorption occurs after the *inhalation* of cannabis smoke. THC is detectable in plasma only seconds after the first puff. Only 15 to 50 percent of the THC in the cannabis cigarette reaches the systemic circulation due to loss by pyrolysis (about 30 percent), remaining THC in the butt (10 to 20 percent), loss by sidestream smoke, and by incomplete absorption and metabolism in the lung. Heavy, experienced smokers show a more than two-fold higher systemic bioavailability than light, occasional smokers resulting from a higher efficiency of inhalation technique. For CBD and CBN a bioavailability of 31 ± 13 percent and 38 percent (mean) has been measured, respectively.

The absorption after *oral* application (for example, as capsules containing a solution of THC in sesame oil) is slow, unpredictable, and erratic and may be increased by using a lipophilic vehicle for the ingestion of THC (such as milk for a cannabis tea). Degradation of THC is possible by stom-

FIGURE 6.1. Pharmacokinetics of THC



Source: Adapted from Harvey DJ. Adsorption, distribution, and biotransformation of the cannabinoids. In Nahas GG, Sutin KM, Harvey D, Agurell S, eds. *Marihuana and medicine.* Totowa, NJ: Humana Press, 1999.

ach acids and in the gut. In the case of Marinol capsules, in which THC is dissolved in sesame oil, the absorption is almost complete. However, an approximate systemic bioavailability of only 10 percent was measured as a result of the extensive first-pass liver metabolism.[5]

The absorption of *rectal* preparations is lower but more constant than with oral formulations. Using THC ester (hemisuccinate) suppositories the bioavailability calculated versus the oral application was about 50 percent.[1]

No pharmacokinetic data from controlled clinical studies are available for the *transdermal* or *sublingual* application of THC.

DISTRIBUTION

In the first distribution phase, THC rapidly penetrates highly vascularized tissues. High concentrations are found in the main distribution sites such as body fat (also a major long-term storage site), liver, heart, lung, gut, kidney,

spleen, mammary gland, placenta, adrenal cortex, thyroid, and pituitary gland at short times after drug administration. The volume of distribution (V) of THC is about 10 liters per kg body weight. Such high V values are typical for lipophilic compounds and clearly indicate the accumulation in deeper compartments. THC and metabolites are almost completely bound to plasma proteins, mainly to lipoproteins (about 60 percent, low-density fraction), albumin and red blood cells (about 10 percent). Only about 3 percent of free THC is found in plasma. For 11-hydroxy-THC (11-OH-THC) a binding rate of 94 to 99 percent has been determined.

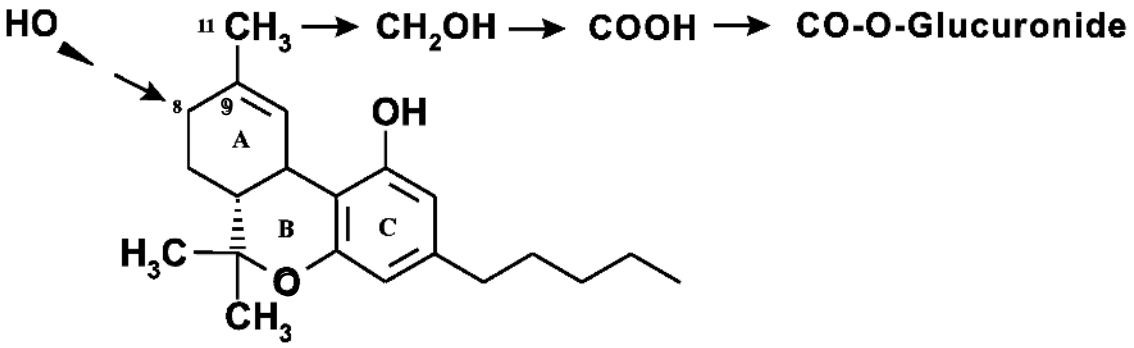
METABOLISM

The metabolic pathway of the cannabinoids is very complex. More than 100 metabolites have been identified for THC alone. The main metabolizing organ is the liver, although other tissues, such as the lungs and the intestines, are also able to biotransform but to a lesser extent. Biotransformation of THC produces mono-, di-, and tri-hydroxy metabolites. Further oxidation results in a series of acids, carbonyl compounds, and their hydroxy derivatives. Microsomal hydroxylation by the cytochrome P-450 isoenzyme CYP2C9 at the allylic carbon atom of ring A leads to 11-OH-THC, which is the main pharmacologically active metabolite of THC, and by the isoenzyme CYP3A to 8-β-hydroxy-THC (see Figure 6.2). Then, 11-OH-THC is oxidized by cytochrome P-450 isozymes to the nonpsychoactive 11-nor-9-carboxy-THC (THC-COOH). A significant first-pass liver effect occurs after oral application, demonstrated by a ratio of 11-OH-THC to THC from 1:2 to 1:1 whereas after *iv* application it is between 1:10 and 1:20. The dominating phase-II metabolite is the O-ester glucuronide of THC-COOH. Conjugates with long-chain fatty acids have a more lipophilic character and are thought to be the form in which THC may be stored within tissues. CBD and CBN are metabolized similarly to THC. CBD inhibits both CPY2C9 and CPY3A but after prolonged administration an induction of CPY3A and other subtypes has been shown.

EXCRETION

Plasma clearance values (CL) of 760 to 1200 ml/min, which are quite similar to the hepatic blood flow, show that THC is eliminated rapidly from the plasma compartment, and the liver plays a major role in the biotransformation. The true elimination half-life of THC is difficult to calculate, as the concentration equilibrium ratio plasma/fatty tissue is only slowly reached, resulting in very low plasma levels which are difficult to analyze. The terminal plasma elimination half-lifes (t1/2) listed in the literature vary

FIGURE 6.2. Main Metabolic Pathways of THC



between one and four days. The complete elimination of one single dosage of THC may require up to five weeks. THC metabolites have been found in urine of frequent cannabis smokers for up to about 80 days after the last consumption. About 80 percent of THC is eliminated by the feces, less than 5 percent of an oral dose of THC as unchanged drug. A pronounced enterohepatic recirculation for THC and metabolites contributes strongly to the slow elimination and 50 to 90 percent of the dose is excreted within the first four to five days. Only traces of THC are excreted in urine, probably due to complete tubular reabsorption. The dominant urinary metabolite is THC-COOH-O-glucuronide with 50 percent excreted in the first day after administration. For monitoring the (ab)use of cannabis the normalization of THC-COOH urine concentrations to urine creatinine concentrations is recommended. In pregnancy, unchanged THC penetrates the placenta and also appears in breast milk. CBD shows a similar urinary excretion pattern with acids and glucuronide conjugates dominating the profile.

PLASMA LEVELS VERSUS ADMINISTRATION ROUTE

The plasma profiles after *inhalation* by smoking a cannabis preparation are similar to the ones after intravenous application (e.g., as ethanolic solution of THC added to a rapidly flowing intravenous saline infusion) but show a greater variability and generally smaller plasma concentrations. Multiple-dose application and frequent cannabis use increase the plasma levels of THC and metabolites and their detectability in plasma. Plasma peaks appear after 3 to 10 min, long before the subject may finish smoking. In general, THC plasma maxima in the range of 100 to 250 ng/ml are measured after smoking cigarettes with 1.75 and 3.25 percent THC, respectively. Maximum plasma concentrations of 50 ng/ml THC ocurred after smoking two cannabis cigarettes, each containing 9 mg THC. A very fast decrease (α elimination phase) of the THC levels is then observed due to distribution into highly vascular tissues, followed by a second, slower

phase (β elimination phase), in which THC is distributed into fatty tissue. Three to five hours after smoking, THC is detectable in plasma only by very sensitive analytical methods. Frequent cannabis smokers attain slightly higher THC plasma levels than infrequent users, because of a more efficient inhalation technique resulting in improved bioavailability. A few minutes after the commencement of smoking 11-OH-THC appears but the plasma levels are only 5 to 10 percent of the THC levels. Within minutes, THC-COOH is also detectable but plasma peaks are about 20 times lower, are less sharp, and are not measured prior to 0.5 to 4 hours after smoking.

Less pronounced plasma curves, lower THC peaks, and a significant interindividual variability can be observed after the *oral* application of THC. As THC is very slowly absorbed from the gastrointestinal tract, the maximum plasma concentrations are measured only after 1 to 6 h. THC plasma peaks of 8 to 9 ng/ml resulted after the oral application of 15 to 20 mg THC dissolved in sesame oil. Due to the extensive first-pass hepatic metabolism the levels of the THC metabolites clearly exceed those of THC. After multiple oral doses of 10 (patient A) and 15 mg THC (patient B) the mean plasma peak of THC was 3.5 and 7.2 ng/ml and of THC-COOH 80 and 185 ng/ml, respectively.[1]

The *rectal* administration route significantly reduces the first-pass liver effect, resulting in much lower THC-COOH plasma levels. After multiple oral doses of 2.5 (patient A) and 5 mg THC hemisuccinate suppositories (patient B), the mean plasma peak of THC was 1.8 and 3.3 ng/ml, appearing 2.5 and 4 h after administration, respectively. The corresponding mean plasma peaks of THC-COOH were 16.4 and 32.7 ng/ml after 6.5 and 4.3 h, respectively.[1]

Two models have been proposed to estimate (e.g., to determine driving under the influence of drugs) the time of the last cannabis consumption for forensic purposes, based on measurements of plasma concentrations. One used THC levels, the other ratios of THC-COOH to THC concentrations in plasma.[3] The authors claimed a prediction within a 95 percent confidence interval. However, the risk of misinterpretation cannot be absolutely excluded[4] (see also Chapter 28).

REFERENCES

1. Brenneisen R, Egli A, ElSohly MA, Henn V, Spiess Y. The effect of orally and rectally administered Δ^9-tetrahydrocannabinol on spasticity: A pilot study with 2 patients. *International Journal of Clinical Pharmacology and Therapeutics* 1996; 34(10):446-452.

2. Harvey DJ. Absorption, distribution, and biotransformation of the cannabinoids. In Nahas GG, Sutin KM, Harvey D, Agurell S, eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999.

3. Huestis M. Pharmacokinetics of THC in inhaled and oral preparations. In Nahas GG, Sutin KM, Harvey D, Agurell S, eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999.

4. Kleiber D, Kovar K-A. *Auswirkungen des Cannabiskonsums*. Stuttgart: Wiss. Verlagsgesellschaft, 1998.

5. Marinol, product information. Columbus, OH: Roxane Laboratories, Inc., 1998.

Chapter 7

Sites and Mechanisms of Action

Roger G. Pertwee

THE ENDOGENOUS CANNABINOID SYSTEM

Because psychotropic cannabinoids have high lipid solubility and low water solubility they were long thought to owe their pharmacological properties to an ability to perturb the phospholipid constituents of biological membranes.[36] Although this mode of action cannot be excluded altogether, it is now clear that for many of the effects of cannabinoids the predominant underlying mechanism is far more specific. More particularly, it is now known that cannabinoids act through receptors: CB_1 receptors (cloned in 1990), and CB_2 receptors (cloned in 1993).[34] Both of these receptor types are coupled through $G_{i/o}$ proteins, negatively to adenylate cyclase and positively to mitogen-activated protein kinase. In addition, CB_1 receptors are coupled to ion channels through $G_{i/o}$ proteins, negatively to N-type and P/Q-type calcium channels and positively to A-type and inwardly rectifying potassium channels. CB_1 receptors may also mobilize arachidonic acid and close 5-HT_3 receptor ion channels[34] and, under certain conditions, activate adenylate cyclase through G_s proteins.[4,17] Another more recent finding is that some CB_1 receptors are negatively coupled to M-type potassium channels.[41] Evidence exists from cat experiments that CB_1 receptors are negatively coupled to voltage-gated dihydropyridine-sensitive L-type calcium channels on cerebral arterial smooth muscle cells.[11]

CB_1 receptors are found in particularly high concentrations within the central nervous system. However, they are also present in certain peripheral organs and tissues. These include some neurons and endocrine glands, leukocytes, spleen, heart, and parts of the reproductive, urinary, and gastrointestinal tracts.[34] Some CB_1 receptors are located at central and peripheral nerve terminals[28,34,48] where they probably modulate neurotransmitter release when activated (see Table 7.1). Although the concentration of CB_1 receptors is considerably less in peripheral tissues than in the central nervous

TABLE 7.1. Inhibition of Transmitter Release by Cannabinoid Receptor Agonists Through CB_1 Receptors in vivo or in vitro

Tissue preparation or brain area	Transmitter-releasing stimulus	Transmitter	References
In vivo			
Rat medial-prefrontal cortex and hippocampus			
	None	ACh*	5,12,13
In vitro			
Rat hippocampal slices	ES	ACh	14,15
Guinea pig intestinal tissue (MPLM)	ES	ACh	8
Guinea pig cerebrocortical slices	ES	NE	40
Human and guinea pig hippocampal slices	ES	NE	40
Guinea pig hippocampal slices	NMDA or kainate	NE	23
Guinea pig hypothalamic slices	ES	NE	40
Guinea pig cerebellar slices	ES	NE	40
Guinea pig retinal discs	ES	NE	39
Rat atria	ES	NE	21
Rat vas deferens	ES	NE	21
Rat striatal slices	NMDA or kainate	DA	23
Rat striatal slices	ES	DA	3
Guinea pig retinal discs	ES	DA	39
Mouse cerebrocortical slices	ES or $K+$	5-HT	22
Mouse hypothalamic slices	ES	5-HT	22
Rat hippocampal slices	ES	GABA	24
Rat striatal slices	ES	GABA#	47
Rat midbrain slices (SNR)	ES or none	GABA#	6,7

Tissue preparation or brain area	Transmitter-releasing stimulus	Transmitter	References
Rostral ventromedial medulla	ES	GABA#	49
Rat primary hippocampal cultured cells	Low [Mg++]o	Glu#	42-45
Rat primary cultured cerebellar granule cells	High KC1	D-Asp	2

Note: ES=electrical stimulation; NMDA=N-methyl-D-aspartate; SNR= substantia nigra pars reticulata; MPLM=myenteric plexus-longitudinal muscle preparation. [Mg++]o=extracellular magnesium concentration; ACh= acetlycholine; NA=norepinephrine; DA=dopamine; 5-HT=5-hydroxytryptamine; GABA=γ-aminobutyric acid, D-Asp=D-aspartate.

* ACh collected by microdialysis. # Indirect electrophysiological evidence for decreased transmitter release.

system, this does not imply that peripheral CB_1 receptors are unimportant. Thus, some peripheral tissues may contain high concentrations of CB_1 receptors, localized in discrete regions such as nerve terminals that form only a small part of the total tissue mass.

Within the central nervous system, the distribution pattern of CB_1 receptors is heterogeneous and can account for several prominent pharmacological properties of CB_1 receptor agonists. For example, evidence shows that the cerebral cortex, hippocampus, and basal ganglia are richly populated with CB_1 receptors and that these receptors mediate the well documented ability of CB_1 receptor agonists to impair cognition and memory and to alter motor function.[18,28,34,38,48] CB_1 receptor agonists are also analgesic, and in line with this property, there is evidence for the presence of CB_1 receptors in several areas of the central nervous system that mediate the perception of pain[30,50] (see also Chapter 8). Cannabinoid-induced analgesia may also be mediated by CB_1 receptors located on the peripheral terminals of primary afferent neurons.[20,30,50]

CB_2 receptors are expressed primarily by immune tissues, for example leukocytes, spleen, and tonsils.[34] More mRNA for CB_2 than CB_1 receptors exists in the immune system, and the level of CB_2 mRNA in human tonsils matches that of CB_1 mRNA in human cerebellum. Levels of CB_1 and CB_2 mRNA in human leukocytes have been shown to vary with cell type (B cells > natural killer cells > monocytes > polymorphonuclear neutrophils, T4 and T8 cells).[10,34] Although CB_2 mRNA has not been detected on neuronal tissue from human or rat

brain,[10,27] there is evidence for its presence in rat brain microglia.[25] One report shows the presence of CB_2 mRNA together with CB_1 mRNA in mouse cerebellar tissue.[46] One possibility yet to be excluded is that the cerebellar tissue used in this study contained microglia and that CB_2 mRNA was present in this immune tissue rather than in the neuronal tissue. The physiological roles of CB_2 receptors are proving difficult to establish.

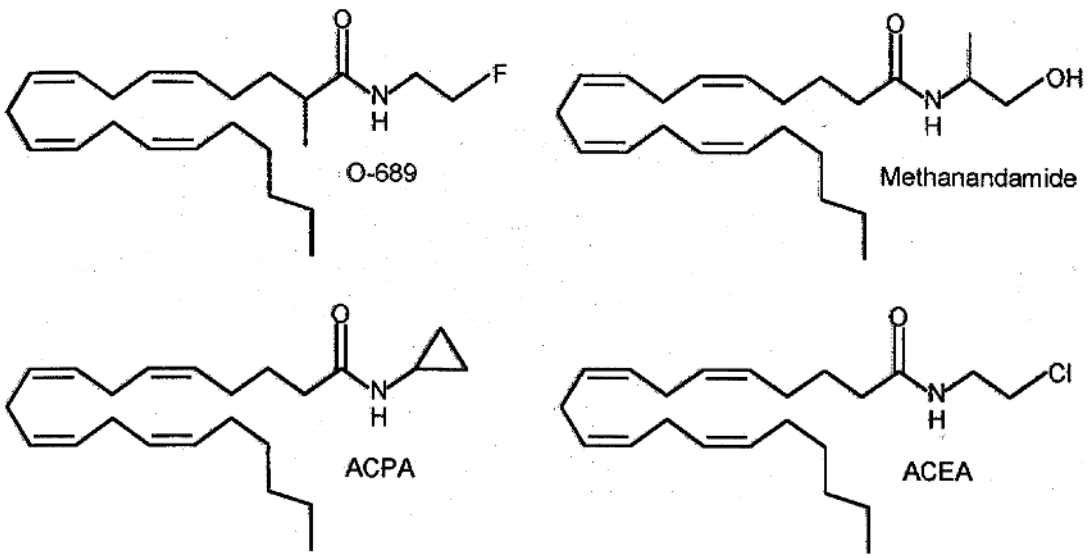
The discovery of cannabinoid receptors was followed in 1992 by the demonstration of the existence of endogenous cannabinoid receptor agonists.[9,29,34] The most important of these are arachidonylethanolamide (anandamide) and 2-arachidonylglycerol (see Figure 2.6), and there is evidence that both of these compounds can serve as neuromodulators or neurotransmitters. This comes from demonstrations that they are synthesized by neurones, that they can undergo depolarization-induced release from neurons and that once released they are rapidly removed from the extracellular space.[9] For anandamide, such removal seems to depend on a carrier-mediated, saturable uptake process present in neurons and astrocytes.[9] Once within the cell, anandamide is presumably hydrolyzed to arachidonic acid and ethanolamine by fatty acid amide hydrolase.[9] This is a microsomal enzyme, found both in neurons and in some nonneuronal tissues, which seems to serve as a general fatty acid amide hydrolase. The same enzyme can also catalyze the hydrolysis of 2-arachidonylglycerol.[9] However, the presence of a transporter for 2-arachidonylglycerol in neuronal membranes has not yet been demonstrated. Indeed, this compound may enter cells by diffusion.[9] Cannabinoid receptors and their endogenous ligands together constitute what is now often referred to as "the endogenous cannabinoid system."

CANNABINOID RECEPTOR LIGANDS

CB_1- and CB_2-Selective Ligands

The availability of CB_1 and CB_2 receptor binding assays has facilitated the development of agonists and antagonists with significant selectivity for CB_1 or CB_2 receptors.[35] More specifically, 2-methylarachidonyl-(2'-fluoroethyl) amide (O-689) and *(R)*-(+)-arachidonyl-1'-hydroxy-2'-propylamide (methanandamide) are both CB_1-selective agonists with respectively 23-fold and 41- or 49-fold greater affinity for CB_1 than CB_2 receptors (see Figure 7.1). They are both structural analogues of anandamide that also have in common the property of being more resistant to enzymic hydrolysis than anandamide.[35] Two agonists with even greater CB_1-selectivity are arachidonylcyclopropylamide (ACPA) and arachidonyl-2'-chloroethylamide (ACEA) (see Figure 7.1).[19,35] These have respectively 325- and >1428-fold higher affinity for CB_1 than CB_2 receptors but seem to lack resistance to enzymic hydrolysis. Other important CB_1-selective ligands are SR141716A and

FIGURE 7.1. Structures of Some Selective CB_1-Selective Agonists



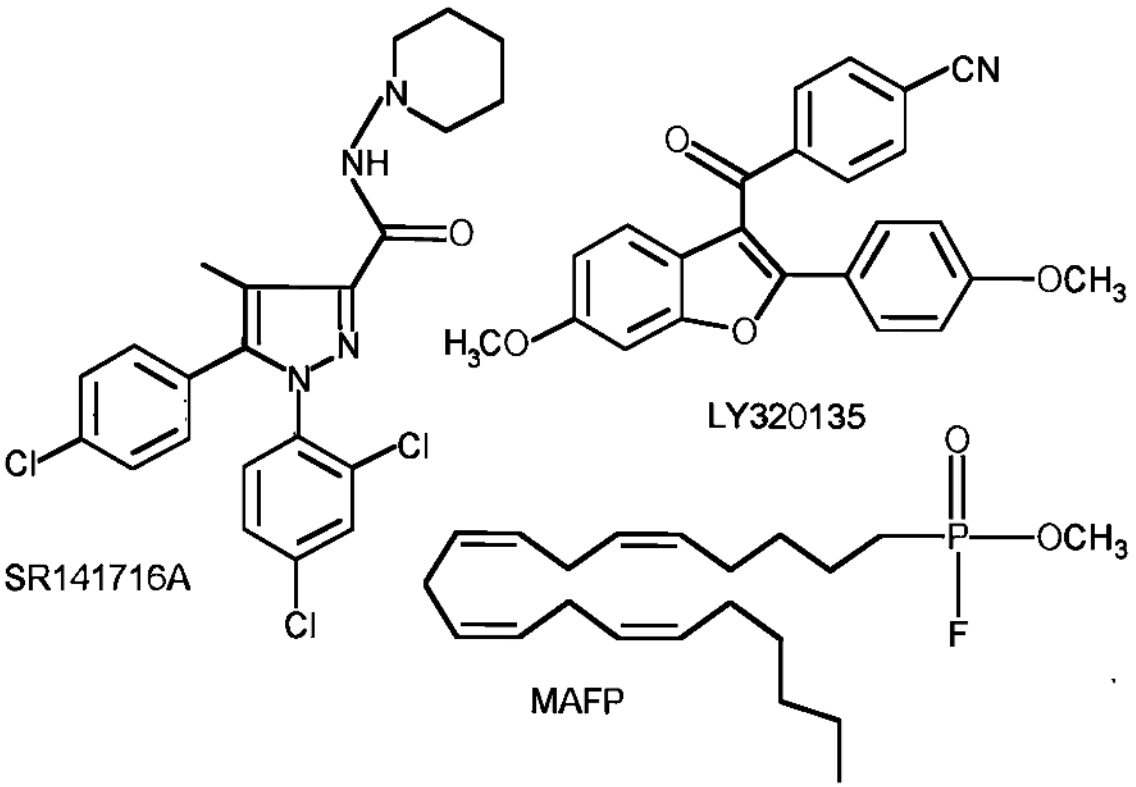
LY320135 (see Figure 7.2), both of which behave as competitive, surmountable antagonists.[29,34,35] Methyl arachidonyl fluorophosphonate is also of interest as it behaves as a competitive, insurmountable, CB_1-receptor antagonist.[35] Whether this agent has significant affinity for CB_2 receptors remains to be established.

Among the most selective and potent ligands for CB_2 receptors to have been developed to date are L-759633, JWH-139, AM630, JWH-133, L-759656, and SR144528. These have respectively at least 163-, 164-, 165-, 199-, 414-, and 728-fold higher affinity for CB_2 than CB_1 receptors.[35] Of these agents, L-759633 and L-759656 are high-efficacy CB_2 receptor agonists,[35] as is JWH-133 (Pertwee and Ross, unpublished). On the other hand, SR144528 and AM630 behave as potent CB_2 receptor antagonists. At high concentrations SR144528 also blocks CB_1 receptors whereas AM630 behaves as a weak partial agonist or weak inverse agonist at CB_1 receptors.[35]

Inverse Cannabimimetic Effects of SR141716A, SR144528, LY320135, and AM630

When administered by themselves, SR141716A, SR144528, LY320135, and AM630 can produce effects in in vivo and in vitro CB_1 or CB_2 bioassay systems that are opposite in direction from those produced by cannabinoid receptor agonists, suggesting that the endogenous cannabinoid system is tonically active in these bioassay systems.[35] This tonic activity may stem from the release of an endogenous cannabinoid receptor agonist that produces cannabimimetic tone susceptible to attenuation by cannabinoid re-

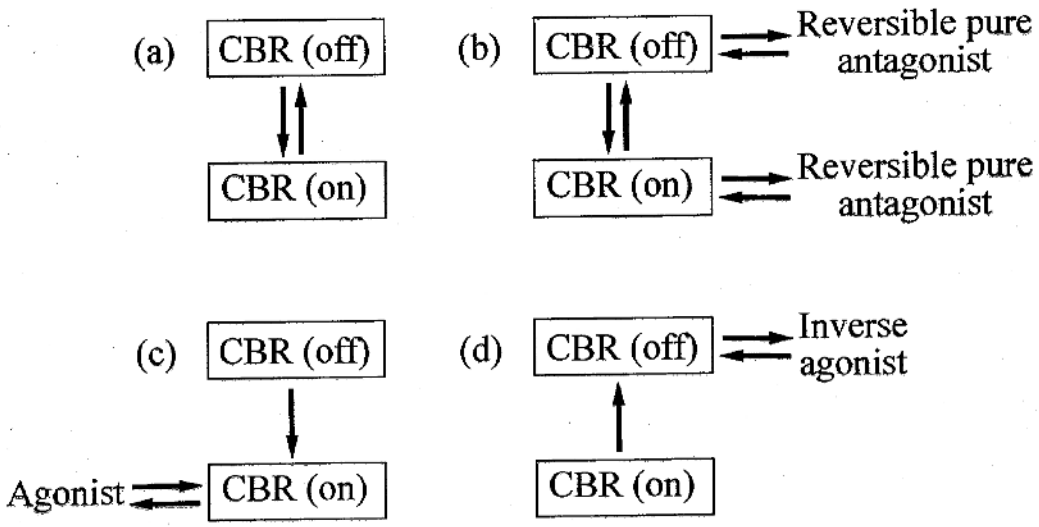
FIGURE 7.2. Structures of Some Selective CB_1-Selective Antagonists



ceptor antagonists. Alternatively, it may arise because a proportion of cannabinoid receptors can exist in a constitutively active, "precoupled" state in which they can activate their effector systems even in the absence of an agonist. According to one model (see Figure 7.3), these precoupled receptors exist in equilibrium with unprecoupled receptors. SR141716A, SR144528, LY320135, and AM630 might then act as inverse agonists rather than as pure antagonists, producing their "inverse cannabimimetic effects" by binding preferentially to the unprecoupled receptors so as to shift the equilibrium away from the receptors in the constitutively active state (see Figure 7.3). These two hypotheses are not mutually exclusive. Indeed, it is possible that tonic activity of the endogenous cannabinoid system stems mainly from endogenous cannabinoid release in some biological systems or experimental protocols, from receptor precoupling in others and from a combination of both mechanisms in yet a third group of biological systems or protocols.

Evidence that release of endogenous cannabinoids does take place in vivo under physiological or pathophysiological conditions already exists.[16,51] Evidence suggests that CB_1 and CB_2 receptors can exist in a precoupled state and that SR141716A and SR144528 are indeed inverse agonists. This evidence has been detailed elsewhere.[35,37] It also seems likely that LY320135

FIGURE 7.3. The Two-State Model of Inverse Agonists



Note: According to this model, (a) a proportion of cannabinoid receptors can exist in two interchangeable states, a constitutively active "on" state in which they can activate the effector system even in the absence of an agonist and an "off" state which is not constitutively active; (b) a pure antagonist has equal affinity for both receptor states, thus leaving the equilibrium between "on" and "off" states unchanged; (c) an agonist has higher affinity for the "on" state thus shifting the equilibrium toward this state; and (d) an inverse agonist has higher affinity for the "off" state thus shifting the equilibrium toward this state. A more complex model to explain the action of cannabinoid receptor agonists has also been proposed.[1]

and AM630 are inverse agonists.[35] For SR141716A and SR144528, the evidence for an inverse agonist action is based largely on data from experiments with cells that have been transfected with CB_1 or CB_2 receptors and therefore have a rather high cannabinoid receptor expression level. The extent to which precoupling occurs in tissues that express cannabinoid receptors naturally remains to be established. Not all cannabinoid receptor-containing systems show signs of tonic activity when exposed to an antagonist.[35] Presumably this reflects an absence from these biological systems of sufficient precoupled receptors and/or of sufficient ongoing endogenous cannabinoid production.

Other Cannabinoid Receptor Ligands

Some cannabinoid receptor ligands that are commonly used as experimental tools differ little in their affinities for CB_1 and CB_2 receptors. These are Δ^9-tetrahydrocannabinol and CP55940 which have approximately equal

affinity for these two receptor types: the aminoalkylindole, WIN55212-2, which shows marginal selectivity for CB_2 receptors, and anandamide, which has marginal selectivity for CB_1 receptors (see Figures 2.4 and 2.5).[35] As to the ability of these ligands to activate cannabinoid receptors, CP55940 and WIN55212-2 both have significantly higher efficacy than Δ^9-tetrahydrocannabinol or anandamide at both CB_1 and CB_2 receptors. The efficacy of Δ^9-tetrahydrocannabinol and anandamide is less at CB_2 than at CB_1 receptors. Indeed, as is to be expected for a low-efficacy (partial) agonist, Δ^9-tetrahydrocannabinol can, depending on the bioassay system that is used, behave either as an agonist or antagonist at CB_2 receptors.[35]

PALMITYLETHANOLAMIDE

This endogenous fatty acid ethanolamide is frequently referred to in the cannabinoid literature as a CB_2 receptor agonist. However, although palmitylethanolamide has been shown to displace [^{3}H]WIN 55,212-2 readily from specific binding sites on the membranes of RBL-2H3 cells which contain CB_2 but not CB_1 mRNA, it has little affinity for CB_2 (or CB_1) receptors present on the membranes of cells that have been transfected with these receptors.[35] It remains possible that palmitylethanolamide activates CB_1 or CB_2 receptors indirectly by inhibiting the metabolism of endogenous cannabinoids[26] and also that it is an agonist for "CB_2-like" receptors, the existence of which remains to be demonstrated.[31,35]

INHIBITORS OF ENDOGENOUS CANNABINOID TISSUE UPTAKE OR METABOLISM

It should be possible to activate the endogenous cannabinoid system not only directly, with cannabinoid receptor agonists, but also indirectly, with drugs that inhibit the tissue uptake or metabolism of endogenous cannabinoids so as to increase the concentration of these cannabinoids at their sites of action. Two important lead compounds for indirect cannabinoid receptor activation are stearyl sulphonyl fluoride (AM381) and *N*-(4-hydroxyphenyl) arachidonylamide (AM404) (see Figure 2.9).[35] AM381 is a potent irreversible inhibitor of fatty acid amide hydrolase, the enzyme that catalyzes the hydrolysis of anandamide and 2-arachidonyl glycerol. It shows considerable separation between potency for inhibition of fatty acid amide hydrolase (EC_{50} = 4 nM) and ability to bind to CB_1 receptors (EC_{50} = 18.5 μM for displacement of [^{3}H]CP55940 from specific binding sites on rat forebrain membranes). AM404 inhibits anandamide uptake, for example by rat cultured cortical neurons, without detectably inhibiting either fatty acid amide hydrolase or the tissue uptake of the anandamide metabolites, arachidonic acid and ethanolamine.[35] It has also been shown to potentiate some in vitro

and in vivo effects of anandamide, for example, anandamide-induced inhibition of forskolin-stimulated cyclic AMP production by rat cultured cortical neurons, anandamide-induced antinociception in the mouse hot plate test, and anandamide-induced hypotension in anaesthetized guinea pigs.[35] Although AM404 binds to CB_1 receptors at similar concentrations to those at which it inhibits anandamide uptake, it does not seem to behave as a direct cannabinoid receptor agonist. Whether its ability to potentiate anandamide is an indication that AM404 does not produce significant antagonism at CB_1 receptors depends on whether the effects of anandamide it potentiates are mediated by CB_1 receptors (see the review by Mechoulam and colleagues[26] and also the next section).

OTHER TYPES OF CANNABINOID RECEPTORS

One important question still to be resolved is whether mammalian tissues contain any as yet undiscovered cannabinoid receptor types or subtypes that are of physiological or clinical importance. Already, a spliced variant of CB_1 cDNA ($CB_{[1a]}$) has been isolated from a human lung cDNA library and three distinct CB_1 mRNAs have been detected in C57BL/6 mouse brain.[52] Evidence exists for a CB_2-like receptor in both the vasa deferentia and hind paws of mice.[31] More recently, evidence has been obtained from experiments with isolated blood vessel preparations that anandamide and methanandamide (but not other cannabinoid receptor ligands) can activate vanilloid receptors on sensory neurons.[52] This intriguing observation raises the possibility that anandamide is an endogenous agonist for vanilloid receptors and hence also that these receptors are perhaps really anandamide receptors or cannabinoid CB_3 receptors. The extent to which exogenously administered or endogenous anandamide can modulate the perception of pain by acting through vanilloid receptors that are known to be present on nociceptive sensory neurons remains to be established.

CONCLUDING DISCUSSION

The recent advances in our understanding of the sites and mechanisms of action of cannabinoids briefly described in this chapter have been paralleled by a growing interest in new clinical applications for cannabinoids. One of the challenges facing those who wish to exploit the therapeutic potential of CB_1 receptor agonists to the full is the need to devise strategies that will reduce or abolish the unwanted central effects of these agents without attenuating their sought-after benefits. Consideration of what is now known about the pharmacology of the endogenous cannabinoid system reveals several possible strategies and these are summarized as follows.

1. One strategy would be to develop therapeutic agents from compounds such as AM381 or AM404 that activate the endogenous cannabinoid system indirectly by selectively inhibiting the tissue uptake or metabolism of endocannabinoids so as to increase their levels at cannabinoid receptors (see previous discussion). These drugs should be more selective than direct agonists as they are unlikely to affect all parts of the endogenous cannabinoid system at one time, producing instead effects only at sites where ongoing production of endogenous cannabinoids is taking place. Just as monoamine levels can be enhanced to combat depression, modulation of endogenous cannabinoid concentrations at their sites of action could prove to be clinically beneficial. Evidence suggests that tonic activity of the endogenous cannabinoid system increases in animal models of neuropathic pain[30] and that noxious stimuli stimulate anandamide production by nociceptive neurons (see previous discussion and Chapter 8). However, the extent to which noxious stimuli also enhance anandamide production by other types of neuron is still to be determined, as is the identity of other types of stimuli which enhance anandamide production in the whole organism.

2. A second strategy for minimizing the unwanted central effects of cannabinoids is to make use of CB_1 receptor partial agonists. These are agents with high affinity for CB_1 receptors but reduced ability (efficacy) to activate these receptors and some have already been developed.[35] The underlying assumption of this strategy is that a therapeutic effect can be achieved with a CB_1 receptor occupancy lower than that required to produce unwanted central effects. This might be because neurons mediating the sought-after therapeutic effect express more CB_1 receptors or contain CB_1 receptors that are more efficiently coupled to their effector systems than neurons mediating the psychotropic effects of cannabinoids. Although the validity of this assumption remains to be established, it is already known that significant regional variations exist within the brain, both in the concentration and in the coupling efficiency of cannabinoid receptors.[35] Moreover, the possibility exists that the increased tonic activity of the endogenous cannabinoid system observed in some animal models of neuropathic pain (see previous discussion) stems at least in part from an increase in the number of constitutively active CB_1 receptors on nociceptive neurons.

3. Another possibility would be to exploit synergistic interactions that are known to occur between cannabinoids and opioids for antinociception or between cannabinoids and benzodiazepines for inhibitory effects on motor function.[30,32,33] Whether such synergism would make it of therapeutic advantage to administer a cannabinoid in combination with an opioid or a benzodiazepine will depend largely on the extent to which the unwanted effects of these drugs are also augmented after combined administration.

4. In view of the evidence that analgesia can be induced by the activation of CB_1 cannabinoid receptors present on sensory neurons outside the brain

or spinal cord (see previous discussion and Chapter 8), it may be worth designing cannabinoids that do not readily cross the blood brain barrier and yet retain the ability to activate CB_1 receptors located outside the central nervous system.

5. Some peripheral neurons seem to express non-CB_1 (CB_2-like) cannabinoid receptors which can mediate antinociception. It may, therefore, also be worth developing agonists that selectively activate these receptors, especially as there is little evidence for the presence of such receptors on central neurons. The possibility that anandamide can produce analgesia by activating vanilloid receptors on peripheral sensory neurons also merits further investigation as these receptors are not expected to mediate the unwanted central effects of CB_1 receptor agonists.

6. Because it is known that CB_1 receptors are present on the terminals of primary afferent neurons and that intrathecal administration of CB_1 receptor agonists induces antinociception in animals,[30] it may be worth administering CB_1 receptor agonists by the intrathecal route. This strategy is already sometimes adopted for baclofen, to reduce the incidence of its adverse effects in multiple sclerosis patients.

7. For Δ^9-tetrahydrocannabinol, one other strategy may be to administer it together with one or more other cannabinoids. Thus there is evidence, albeit somewhat limited, that Δ^9-tetrahydrocannabinol is more effective as an analgesic and induces fewer or less intense unwanted effects when administered together with cannabidiol or cannabichromene than when administered alone.[30,33]

REFERENCES

1. Bouaboula M, Perrachon S, Milligan L, Canat X, Rinaldi-Carmona M, Portier M, Barth F, Calandra B, Pecceu F, Lupker J, et al. A selective inverse agonist for central cannabinoid receptor inhibits mitogen-activated protein kinase activation stimulated by insulin or insulin-like growth factor 1. Evidence for a new model of receptor/ligand interactions. *Journal of Biological Chemistry* 1997;272(35): 22330-22339.

2. Breivogel CS, Walker JM, Huang S, Childers SR. Cannabinoid signalling in cultured rat cerebellar granule cells. In *1999 Symposium on the Cannabinoids*. Burlington, VT: International Cannabinoid Research Society, 1999, p. 19.

3. Cadogan A-K, Alexander SPH, Boyd EA, Kendall DA. Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. *Journal of Neurochemistry* 1997;69(3):1131-1137.

4. Calandra B, Portier M, Kernéis A, Delpech M, Carillon C, Le Fur G, Ferrara P, Shire D. Dual intracellular signaling pathways mediated by the human cannabinoid CB_1 receptor. *European Journal of Pharmacology* 1999;374(3):445-455.

5. Carta G, Nava F, Gessa GL. Inhibition of hippocampal acetylcholine release after acute and repeated Δ^9-tetrahydrocannabinol in rats. *Brain Research* 1998; 809(1):1-4.

6. Chan PKY, Chan SCY, Yung W-H. Presynaptic inhibition of GABAergic inputs to rat substantia nigra pars reticulata neurones by a cannabinoid agonist. *Neuroreport* 1998;9(4):671-675.

7. Chan PKY, Yung W-H. Occlusion of the presynaptic action of cannabinoids in rat substantia nigra pars reticulata by cadmium. *Neuroscience Letters* 1998; 249(1):57-60.

8. Coutts AA, Pertwee RG. Inhibition by cannabinoid receptor agonists of acetylcholine release from the guinea pig myenteric plexus. *British Journal of Pharmacology* 1997;121(8):1557-1566.

9. Di Marzo V, Melck D, Bisogno T, De Petrocellis L. Endocannabinoids: Endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends In Neuroscience* 1998;21(12):521-528.

10. Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry* 1995;232:54-61.

11. Gebremedhin D, Lange AR, Campbell WB, Hillard CJ, Harder DR. Cannabinoid CB_1 receptor of cat cerebral arterial muscle functions to inhibit L-type Ca^{2+} channel current. *American Journal of Physiology* (Heart Circulation Physiology 45) 1999;276:H2085-H2093.

12. Gessa GL, Casu MA, Carta G, Mascia MS. Cannabinoids decrease acetylcholine release in the medial-prefrontal cortex and hippocampus, reversal by SR 141716A. *European Journal of Pharmacology* 1998;355(2-3):119-124.

13. Gessa GL, Mascia MS, Casu MA, Carta G. Inhibition of hippocampal acetylcholine release by cannabinoids: Reversal by SR 141716A. *European Journal of Pharmacology* 1997;327(1):R1-R2.

14. Gifford AN, Ashby CR. Electrically evoked acetylcholine release from hippocampal slices is inhibited by the cannabinoid receptor agonist, WIN 55212-2, and is potentiated by the cannabinoid antagonist, SR 141716A. *Journal of Pharmacology and Experimental Therapeutics* 1996;277(3):1431-1436.

15. Gifford AN, Samiian L, Gatley SJ, Ashby CR. Examination of the effect of the cannabinoid receptor agonist, CP 55,940, on electrically evoked transmitter release from rat brain slices. *European Journal of Pharmacology* 1997;324(2-3):187-192.

16. Giuffrida A, Parsons LH, Kerr TM, de Fonseca FR, Navarro M, Piomelli D. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. *Nature Neuroscience* 1999;2(4):358-363.

17. Glass M, Felder CC. Concurrent stimulation of cannabinoid CB_1 and dopamine D_2 receptors augments cAMP accumulation in striatal neurons: Evidence for a G_s linkage to the CB_1 receptor. *Journal of Neuroscience* 1997;17(19):5327-5333.

18. Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. *Life Sciences* 1999;65(6-7):715-723.

19. Hillard CJ, Manna S, Greenberg MJ, Dicamelli R, Ross RA, Stevenson LA, Murphy V, Pertwee RG, Campbell WB. Synthesis and characterization of potent and selective agonists of the neuronal cannabinoid receptor (CB_1). *Journal of Pharmacology and Experimental Therapeutics* 1999;289(3):1427-1433.

20. Hohmann AG, Herkenham M. Cannabinoid receptors undergo axonal flow in sensory nerves. *Neuroscience* 1999;92(4):1171-1175.

21. Ishac EJN, Jiang L, Lake KD, Varga K, Abood ME, Kunos G. Inhibition of exocytotic noradrenaline release by presynaptic cannabinoid CB_1 receptors on peripheral sympathetic nerves. *British Journal of Pharmacology* 1996;118:2023-2028.

22. Kathmann M, Nakazi M, Bauer U, Schlicker E. WIN 55212-2 inhibits serotonin release in the mouse brain cortex via presynaptic cannabinoid CB_1 receptors. In *1999 Symposium on the Cannabinoids*. Burlington, VT: International Cannabinoid Research Society, 1999, p. 51.

23. Kathmann M, Bauer U, Schlicker E, Gothert M. Cannabinoid CB_1 receptor-mediated inhibition of NMDA- and kainate-stimulated noradrenaline and dopamine release in the brain. *Naunyn-Schmiedebergs Archives of Pharmacology* 1999; 359(6):466-470.

24. Katona I, Sperlágh B, Sik A, Käfalvi A, Vizi ES, Mackie K, Freund TF. Presynaptically located CB_1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. *Journal of Neuroscience* 1999;19(11):4544-4558.

25. Kearn CS, Hillard C. A model for the study of cannabinoid actions in microglia. In *1999 Symposium on the Cannabinoids*. Burlington, Vermont: International Cannabinoid Research Society, 1999, p. 44.

26. Mechoulam R, Fride E, Di Marzo V. Endocannabinoids. *European Journal of Pharmacology* 1998;359(1):1-18.

27. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993;365(6441):61-65.

28. Ong WY, Mackie K. A light and electron microscopic study of the CB_1 cannabinoid receptor in primate brain. *Neuroscience* 1999;92(4):1177-1191.

29. Pertwee RG. Advances in cannabinoid receptor pharmacology. In Brown DT, ed. *Cannabis. The Genus Cannabis*. New York: Harwood Academic Publishers, 1998, pp. 125-174.

30. Pertwee RG. Cannabinoids. In Bountra C, Mungali R, Schmidt W, eds. *Current Understanding, Emerging Therapies, and Novel Approaches to Drug Discovery*. New York: Marcel Dekker Inc. In press.

31. Pertwee RG. Evidence for the presence of CB_1 cannabinoid receptors on peripheral neurones and for the existence of neuronal non-CB_1 cannabinoid receptors. *Life Sciences* 1999;65(6-7):597-605.

32. Pertwee RG. *In vivo* interactions between psychotropic cannabinoids and other drugs involving central and peripheral neurochemical mediators. In Murphy

L, Bartke A, eds. *Marijuana/Cannabinoids. Neurobiology and Neurophysiology.* Boca Raton, FL: CRC Press, 1992, pp. 165-218.

33. Pertwee RG. Neuropharmacology and therapeutic potential of cannabinoids. *Addiction Biology* 2000; 5:37-46.

34. Pertwee RG. Pharmacology of cannabinoid CB_1 and CB_2 receptors. *Pharmacology and Therapeutics* 1997;74(2):129-180.

35. Pertwee RG. Pharmacology of cannabinoid receptor ligands. *Current Medicinal Chemistry* 1999;6(8):635-664.

36. Pertwee RG. The central neuropharmacology of psychotropic cannabinoids. *Pharmacology and Therapeutics* 1988;36(2-3):189-261.

37. Portier M, Rinaldi-Carmona M, Pecceu F, Combes T, Poinot-Chazel C, Calandra B, Barth F, Le Fur G, Casellas P. SR 144528, an antagonist for the peripheral cannabinoid receptor that behaves as an inverse agonist. *Journal of Pharmacology and Experimental Therapeutics* 1999;288(6-7):582-589.

38. Sañudo-Peña MC, Tsou K, Walker JM. Motor actions of cannabinoids in the basal ganglia output nuclei. *Life Sciences* 1999;65(6-7):703-713.

39. Schlicker E, Timm J, Göthert M. Cannabinoid receptor-mediated inhibition of dopamine release in the retina. *Naunyn-Schmiedebergs Archives of Pharmacology* 1996;354(6):791-795.

40. Schlicker E, Timm J, Zentner J, Göthert M. Cannabinoid CB_1 receptor-mediated inhibition of noradrenaline release in the human and guinea pig hippocampus. *Naunyn-Schmiedebergs Archives of Pharmacology* 1997;356(5):583-589.

41. Schweitzer P. Cannabinoids decrease the K^+ M-current in hippocampal CA_1 neurons. *Journal of Neuroscience* 2000;20(1):51-58.

42. Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *Journal of Neuroscience* 1996;16(14):4322-4334.

43. Shen M, Thayer SA. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. *Molecular Pharmacology* 1998;54(3):459-462.

44. Shen M, Thayer SA. The cannabinoid agonist WIN 55,212-2 inhibits calcium channels by receptor-mediated and direct pathways in cultured rat hippocampal neurons. *Brain Research* 1998;783(1):77-84.

45. Shen M, Thayer SA. Δ^9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. *Molecular Pharmacology* 1999;55(1):8-13.

46. Skaper SD, Buriani A, Dal Toso R, Petrelli L, Romanello S, Facci L, Leon A. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proceedings of the National Academy of Sciences of the United States of America* 1996;93(9):3984-3989.

47. Szabo B, Dörner L, Pfreundtner C, Nörenberg W, Starke K. Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus striatum. *Neuroscience* 1998;85(2):395-403.

48. Tsou K, Brown S, Sañudo-Peña MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB_1 receptors in the rat central nervous system. *Neuroscience* 1998;83(2):393-411.

49. Vaughan CW, McGregor IS, Christie MJ. Cannabinoid receptor activation inhibits GABAergic neurotransmission in rostral ventromedial medulla neurons in vitro. *British Journal of Pharmacology* 1999;127(4):935-940.

50. Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. The neurobiology of cannabinoid analgesia. *Life Sciences* 1999;65(6-7):665-673.

51. Walker JM, Huang SM, Strangman NM, Tsou K, Sañudo-Peña MC. Pain modulation by release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96(21): 12198-12203.

52. Zygmunt PM, Petersson J, Andersson DA, Chuang H, Sørgård M, Di Marzo V, Julius D, Högestätt ED. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature* 1999;400(6743):452-457.

Chapter 8

Mechanisms of Cannabinoid Analgesia

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MacDonald J. Christie

PHARMACOLOGICAL ACTIONS OF CANNABIS SATIVA

The use of preparations from the plant *Cannabis sativa,* including marijuana and hashish, as natural therapeutic agents has a long history.[33] The isolated psychoactive constituent of *Cannabis sativa,* Δ^9-tetrahydrocannabinol (Δ^9-THC) and a number of synthetic cannabinoid ligands produce pharmacological effects with potential therapeutic applications in the treatment of pain, nausea and vomiting, muscle spasticity, appetite stimulation, and glaucoma. This chapter focuses on providing a description of the anatomical and cellular substrates underlying the pain relieving, or analgesic, actions of cannabinoids.

DO CANNABINOIDS HAVE ANALGESIC ACTIVITY?

Delta-9-THC inhibits the acute nociceptive responses to noxious thermal, mechanical, and chemical stimuli in a number of species.[4,6,35,38,44,53-55] In addition, a number of synthetic cannabinoid ligands, including nabilone, WIN55,212, CP55,940 and HU-210 produce analgesia.[5,10,17,21,25,51,53,54,55] However, the measurement of analgesia in these studies is complicated by the other pharmacological actions of cannabinoids, which include hypothermia, hypomotility, and catalepsy.

Evidence suggests that cannabinoids might be more effective at relieving the hyperalgesia (enhancement of pain sensitivity) and allodynia (pain arising with nonnoxious stimuli) associated with chronic pain states following nerve injury, and visceral and somatic inflammation.[17,22,23,35,39]

AN ENDOGENOUS CANNABINOID PAIN CONTROL SYSTEM

Research into cannabinoids has followed a path similar to that of opioids, leading from isolation of the psychoactive ingredients of plant-based products to the identification of an endogenous neurotransmitter system (see Chapter 7).

Cannabinoids Produce Analgesia at Both Central and Peripheral Sites

Within the central nervous system, cannabinoids, like opioids, act at both spinal (intrathecal) and supraspinal (intracerebroventricular) levels to produce analgesia.[25,30,54] Cannabinoid-induced analgesia is not mediated by opioid receptors because it is unaffected by opioid antagonists.[7,15,21,51,53,54] However, cannabinoid and opioid agonists have synergistic analgesic effects.[38,42,53]

The pharmacological characterization of the actions of Δ^9-THC and synthetic cannabinoid agonists has only recently been made possible with the production of selective CB_1 (SR141716) and CB_2 (SR144528) receptor antagonists.[40,41] The central analgesic and antihyperalgesic actions of cannabinoids are largely mediated by CB_1 receptors because they are reversed by SR141716[17,26,34,40,42,51] and not by SR144528.[7] In addition, cannabinoid analgesia is abolished in rats by pretreatment with oligonucleotides directed against CB_1 mRNA,[12] and in mice with a targeted deletion of the CB_1 receptor.[55]

In the periphery, cannabinoid agonists produce analgesia by acting on both CB_1 and CB_2 receptors.[7] Local injection of cannabinoid agonists into the injured tissue reduces the hyperalgesia associated with visceral and somatic inflammatory pain. WIN55,212 inhibition of pain behavior produced by the formalin test is reversed by both SR141716 and SR144528.[7] The relief of persistent visceral and somatic inflammatory pain by cannabinoids could be potentiated by an anti-inflammatory action.[7,10,22,39,44] It has been suggested that the inflammatory action is mediated by peripheral CB_1 and CB_2 receptors on neuronal and nonneuronal cells, although direct cyclooxygenase inhibition cannot be excluded.

Endogenous Cannabinoids Produce Analgesia

The endogenous cannabinoid anandamide produces analgesia, although it is less efficacious than Δ^9-THC and synthetic agonists.[1,8,14,39,43,51] The reduced efficacy of anandamide is the result of a breakdown which occurs within cells after uptake by a selective transport system.[11] Thus, the anti-

nociceptive action of anandamide is enhanced by enzyme inhibitors[8] and by the recently developed anandamide transport inhibitor, AM404.[3]

Although both synthetic and endogenous cannabinoids bind to brain CB_1 receptors, anandamide-induced analgesia is not completely reversed by the CB_1 antagonist SR141716.[1,8] These findings have led to the suggestion that some of the actions of endogenous cannabinoids are mediated by their metabolites, or via nonreceptor mechanisms. Alternatively, the systemic actions of anandamide might be mediated by peripheral CB_1 and CB_2 receptors.7,22 The inhibition of pain in the formalin test by the endogenous cannabinoids anandamide and palmitylethanolamide is reversed by SR141716 and SR144528.7,22,39

Evidence of tonic endogenous cannabinoid release in chronic pain states exists. Administration of both cannabinoid CB_1 and CB_2 antagonists to animals with induced persistent somatic pain produces hyperalgesia.[7,45]

CANNABINOIDS AND CENTRAL ANALGESIC PATHWAYS

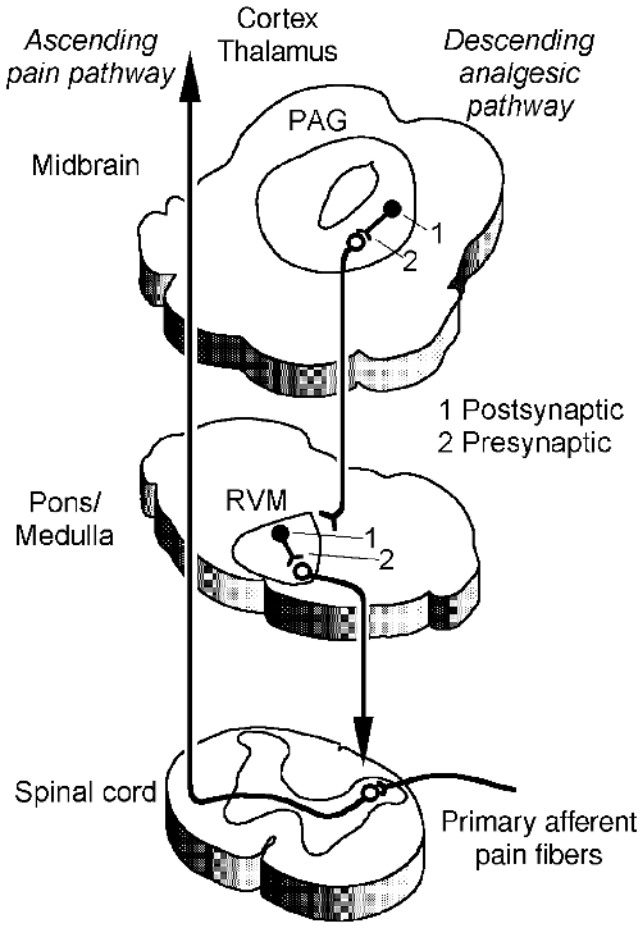
Analgesic drugs, particularly opioids, produce their effects within ascending and descending pain pathways. Anatomical, functional, and electrophysiological evidence indicates that cannabinoids also produce analgesia by acting on neurons within these pain pathways.

Ascending Nociceptive Pathways

Ascending pain pathways arise from nociceptive primary afferent fibers which enter the spinal cord and terminate within the dorsal horn (see Figure 8.1). The spinal cord, a major site of cannabinoid analgesia, is the initial relay point of ascending information and the lowest point of action of the descending antinociceptive pathways. Ascending nociceptive information is conveyed via a number of pathways including the spinothalamic tract, which arises from nociceptive-specific and wide-dynamic range neurons within the spinal dorsal horn and terminates within specific thalamic nuclei.

Like opioids, binding sites for cannabinoids are on the terminals of primary afferents and on neurons within the spinal dorsal horn.[18] However, cannabinoid receptors are expressed in fewer substance-P-containing primary afferent cell bodies and terminals, which are thought to be nociceptors.[19] Cannabinoid CB_1 receptors are also present within higher relay centers, including the thalamus and cortex.[16,27,47] Thus, in addition to a spinal site of action, microinjection of cannabinoids into specific thalamic nuclei produces analgesia.[28]

FIGURE 8.1. Ascending and Descending Pain Pathways



Note: On the left is the major ascending pain pathway (spinothalamic tract). Primary afferent fibers synapse onto spinal cord dorsal horn neurons that project to the thalamus. On the right is the major descending analgesic pathway, which projects via the PAG and RVM to the spinal cord dorsal horn. Analgesia at the spinal level is produced by indirect activation (disinhibition) of the descending projection neurons in PAG and RVM. Disinhibition occurs by reducing the inhibitory influence of GABAergic neurons (filled) on the output projection neurons (open) by (1) postsynaptic inhibition of the cell bodies of GABAergic neurons, and (2) presynaptic inhibition of transmitter release from the terminals of the GABAergic neurons.

Descending Antinociceptive Pathways

Descending antinociceptive pathways project from a number of higher structures to the midbrain periaqueductal grey (PAG), which in turn projects to the serotonergic rostral ventromedial medulla (RVM) and then to the dorsal horn of the spinal cord (see Figure 8.1). Cannabinoid CB_1 receptors are present within all of these brain regions.[16,27,32,47] The PAG is of particular

interest because it is organized into discrete columns which integrate distinct behavioral, somatic, and autonomic responses of an animal to threat, stress, and pain.[2] It has recently been demonstrated that pain of superficial origin, which activates a subpopulation of PAG neurons,[2] increases the release of anandamide within the PAG.[52]

The PAG-RVM-spinal cord serotonergic descending pathway plays a crucial role in the analgesic actions of opioids and cannabinoids. Like opioids, microinjection of cannabinoids into the PAG and RVM produces SR141716 reversible antinociception.[24,28,31,34,52] In addition, lateral descending noradrenergic analgesic pathways (e.g., from A5 cell group) also project to the spinal cord and mediate cannabinoid analgesia.[28]

Cannabinoids Modulate Neuronal Activity in Central Pain Pathways

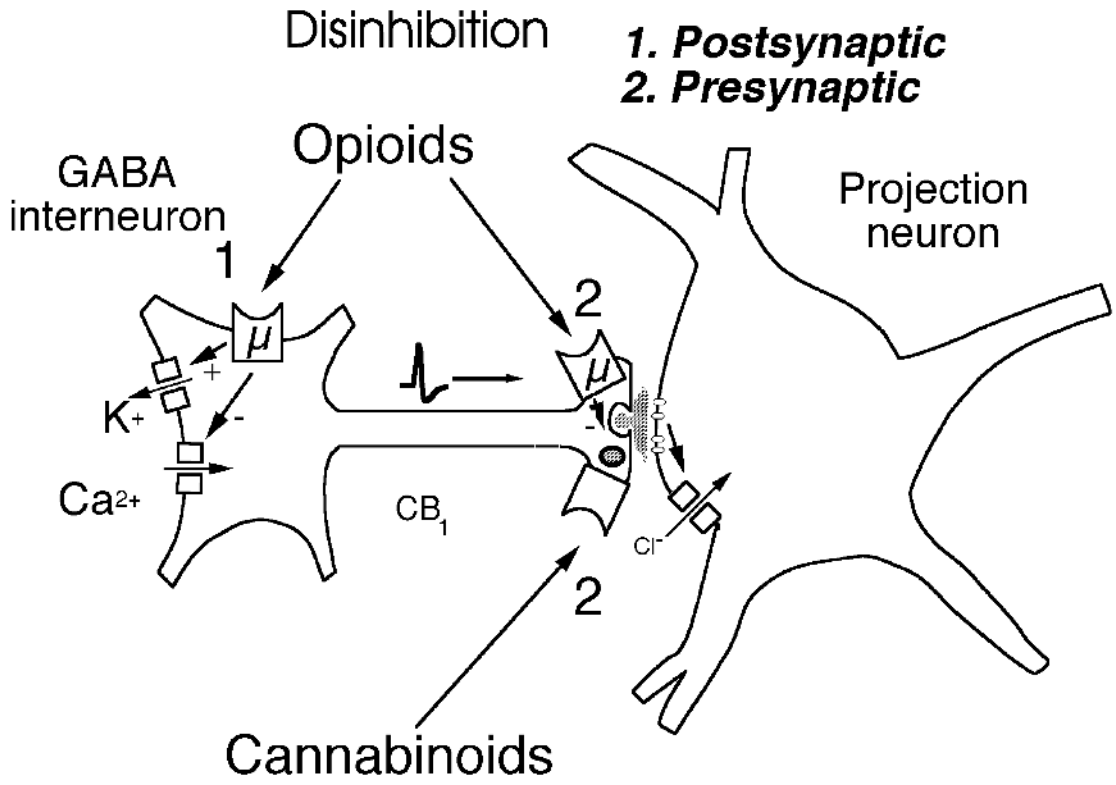
In vivo electrophysiological studies indicate that, like opioids, cannabinoids suppress the activity of neurons involved in the ascending transmission of nociceptive information. Systemic administration of cannabinoid agonists inhibits noxious stimulus-evoked firing, but has no effect on non-noxious stimulus-evoked firing in neurons of the spinal cord dorsal horn and thalamus.[20,29,46] Cannabinoids also inhibit windup (a neuronal correlate of hyperalgesia), which is the augmentation of the response of spinal neurons to repetitive noxious electrical stimuli.[46]

Cannabinoids modulate the activity of neurons in descending antinociceptive pathways. Within the RVM two types of neurons have been characterized which respond to opioids and noxious stimuli.[13] Direct inhibition of one population of RVM neurons by μ-opioids ("on" cells which display increased firing immediately before and during tail-flick responses) and disinhibition of another population ("off" cells which display decreased firing prior to and during tail-flick responses) is associated with opioid antinociception. Systemic administration of cannabinoids inhibits the "on" cell burst and the "off" cell pause in activity associated with the tail-flick response.[34]

CELLULAR ACTIONS OF CANNABINOIDS IN PAIN PATHWAYS

The cellular actions of μ-opioids within the ascending and descending pain pathways have been well characterized. We have recently begun to characterize the cellular actions of cannabinoids within descending pain pathways (see Figure 8.2). There are no studies to date on the cellular actions of cannabinoids on neurons within brain regions which relay ascending pain information.

FIGURE 8.2. Cellular Mechanisms for Pre- and Postsynaptic Disinhibition



Note: (1) Opioids activate μ-receptors to activate a K^+ conductance and inhibit Ca^{2+} conductances to reduce cell body excitability of GABAergic interneurons, which results in reduced action potential firing and reduced GABA release. (2) Cannabinoids activate CB_1 receptors and opioids activate μ-receptors on the terminals of GABAergic neurons to reduce the probability of release of transmitter.

Presynaptic and Postsynaptic Actions?

μ-Opioids directly inhibit subpopulations of presumptive GABAergic interneurons within the PAG and RVM by increasing a K^+ conductance and inhibiting Ca^{2+} conductances.[9,36,37] In contrast to μ-opioids, we have demonstrated that cannabinoid agonists have no direct somatic effects on ion conductances of PAG and RVM neurons.[48,50]

Like μ-opioids,[37,49] cannabinoid agonists inhibit action potentials evoked by GABAergic synaptic transmission in the PAG and RVM.[48,50] The endogenous cannabinoid anandamide also inhibits GABAergic synaptic transmission within the PAG, however, only in the presence of the cannabinoid uptake inhibitor, AM404.[48] Thus, the efficacy of anandamide in PAG is limited by uptake and breakdown.[3] The actions of cannabinoid agonists and anandamide in PAG and RVM are reversed by SR141716.

Opioid and cannabinoid inhibition of GABAergic synaptic transmission in PAG and RVM is mediated by presynaptic inhibition of transmitter release from the terminals of GABAergic neurons.[48,50] Although the mechanism of cannabinoid presynaptic inhibition of GABAergic synaptic transmission is unknown, μ-opioid presynaptic inhibition in PAG is mediated by a PLA_2/lipoxygenase second messenger cascade.[49] This provides a possible substrate for opioid/cannabinoid/cyclooxygenase synergistic analgesic actions.

How Do These Cellular Actions Produce Analgesia?

The PAG forms a component of a descending inhibitory network that, via the RVM, modulates nociceptive neurotransmission at the level of the dorsal horn of the spinal cord (see Figure 8.1). Activation of descending output projection neurons in the PAG and RVM is thought to produce inhibition of nociceptive neurotransmission within the spinal cord dorsal horn. It was originally proposed that μ-opioids produce antinociception within PAG and RVM by reducing inhibitory GABAergic influences on descending projection neurons.[13] This *disinhibition* leads to increased activity of descending output projection neurons in PAG and RVM, thereby activating the analgesic pathway to the spinal cord.

Our recent findings indicate that while opioids and cannabinoids act on the terminals of GABAergic neurons to inhibit transmitter release (presynaptic), only opioids directly inhibit the cell bodies of GABAergic neurons (postsynaptic) in PAG and RVM (see Figure 8.2). Both pre- and postsynaptic mechanisms act to reduce inhibitory GABAergic influences and the resultant *disinhibition* underlies the excitatory actions of these agents on descending antinociceptive pathways.

SUMMARY

It is now becoming apparent that, like opioids, cannabinoids act via specific receptors within pain pathways to produce analgesia. The distinct anatomical distributions and effects of cannabinoids and opioids on both ascending and descending pain pathways suggests that they may be useful for management of different pain states. The distinction between cannabinoids and opioids is emphasized by more recent electrophysiological studies and provides a cellular basis for their synergistic analgesic actions. These findings suggest that cannabinoids warrant urgent study as therapeutic agents, particularly with the emergence of novel cannabinoid drugs.

REFERENCES

1. Adams IB, Compton DR, Martin BR. Assessment of anandamide interaction with the cannabinoid brain receptor: SR 141716A antagonism studies in mice and autoradiographic analysis of receptor binding in rat brain. *Journal of Pharmacology and Experimental Therapeutics* 1998;284(3):1209-1217.

2. Bandler R, Shipley MT. Columnar organization in the midbrain periaqueductal gray: Modules for emotional expression? *Trends in Neuroscience* 1994;17(9):379-389.

3. Beltramo M, Stella N, Calignano A, Lin SY, Makriyannis A, Piomelli D. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. *Science* 1997;277(5329):1094-1097.

4. Bicher HI, Mechoulam R. Pharmacological effects of two active constituents of marihuana. *Archives Internationales de Pharmacodynamie et de Therapie* 1968; 172(1):24-31.

5. Bloom AS, Dewey WL, Harris LS, Brosius KK. 9-nor-9?-hydroxyhexahydrocannabinol, a cannabinoid with potent antinociceptive activity: Comparisons with morphine. *Journal of Pharmacology and Experimental Therapeutics* 1977;2002: 263-270.

6. Buxbaum DM. Analgesic activity of Δ^9-tetrahydrocannabinol in the rat and mouse. *Psychopharmacologia* 1972;25(3):275-280.

7. Calignano A, La Rana G, Giuffrida A, Piomelli D. Control of pain initiation by endogenous cannabinoids. *Nature* 1998;394(6690):277-281.

8. Compton DR, Martin BR. The effect of the enzyme inhibitor phenylmethylsulfonyl fluoride on the pharmacological effect of anandamide in the mouse model of cannabimimetic activity. *Journal of Pharmacology and Experimental Therapeutics* 1997;283(3):1138-1143.

9. Connor M, Christie MJ. Modulation of Ca^{2+} channel currents of acutely dissociated rat periaqueductal grey neurons. *Journal of Physiology* 1998;509(Pt1):47-58.

10. Dajani EZ, Larsen KR, Taylor J, Dajani NE, Shahwan TG, Neeleman SD, Taylor MS, Dayton MT, Mir GN. 1',1'-Dimethylheptyl-delta-8-tetrahydrocannabinol-11-oic acid: A novel, orally effective cannabinoid with analgesic and anti-inflammatory properties. *Journal of Pharmacology and Experimental Therapeutics* 1999;291(1):31-38.

11. Di Marzo V, Fontana A, Cadas H, Schinelli S, Cimino G, Schwartz JC, Piomelli D. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature* (London) 1994;372(6507):686-691.

12. Edsall SA, Knapp RJ, Vanderah TW, Roeske WR, Consroe P, Yamamura HI. Antisense oligodeoxynucleotide treatment to the brain cannabinoid receptor inhibits antinociception. *Neuroreport* 1996;7(2):593-596.

13. Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. *Annual Review of Neuroscience* 1991;14:219-245.

14. Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. *European Journal of Pharmacology* 1993;231(2):313-314.

15. Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors [letter]. *Lancet* 1999;353(9152):560.

16. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. *Journal of Neuroscience* 1991;11(2):563-583.

17. Herzberg U, Eliav E, Bennett GJ, Kopin IJ. The analgesic effects of R(+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neuroscience Letters* 1997;221(2-3):157-160.

18. Hohmann AG, Briley EM, Herkenham M. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Research* 1999; 822(1-2):17-25.

19. Hohmann AG, Herkenham M. Localization of central cannabinoid CB_1 receptor messenger RNA in neuronal subpopulations of rat dorsal root ganglia: A double-label in situ hybridization study. *Neuroscience* 1999;90(3):923-931.

20. Hohmann AG, Tsou K, Walker JM. Cannabinoid suppression of noxious heat-evoked activity in wide dynamic range neurons in the lumbar dorsal horn of the rat. *Journal of Neurophysiology* 1999;81(2):575-583.

21. Jacob JJ, Ramabadran K, Campos-Medeiros M. A pharmacological analysis of levonantradol antinociception in mice. *Journal of Clinical Pharmacology* 1981; 21:327S-333S.

22. Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB_2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998;76(1-2):189-199.

23. Li J, Daughters RS, Bullis C, Bengiamin R, Stucky MW, Brennan J, Simone DA. The cannabinoid receptor agonist WIN 55,212-2 mesylate blocks the development of hyperalgesia produced by capsaicin in rats. *Pain* 1999;81(1-2):25-33.

24. Lichtman AH, Cook SA, Martin BR. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: Evidence supporting periaqueductal gray involvement. *Journal of Pharmacology and Experimental Therapeutics* 1996; 276(2):585-593.

25. Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. *Journal of Pharmacology and Experimental Therapeutics* 1991;258(2):517-523.

26. Lichtman AH, Martin BR. The selective cannabinoid antagonist SR 141716A blocks cannabinoid-induced antinociception in rats. *Pharmacology, Biochemistry and Behavior* 1997;57(1-2):7-12.

27. Mailleux P, Vanderhaeghen JJ. Distribution of neuronal cannabinoid receptor in the adult rat brain: A comparative receptor binding radioautography and in situ hybridization histochemistry. *Neuroscience* 1992;48(3):655-668.

28. Martin WJ, Coffin PO, Attias E, Balinsky M, Tsou K, Walker JM. Anatomical basis for cannabinoid-induced antinociception as revealed by intracerebral microinjections. *Brain Research* 1999;822(1-2):237-242.

29. Martin WJ, Hohmann AG, Walker JM. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus by a cannabinoid agonist: correlation between electrophysiological and antinociceptive effects. *Journal of Neuroscience* 1996;16(20):6601-6611.

30. Martin WJ, Lai NK, Patrick SL, Tsou K, Walker JM. Antinociceptive actions of cannabinoids following intraventricular administration in rats. *Brain Research* 1993;629(2):300-304.

31. Martin WJ, Patrick SL, Coffin PO, Tsou K, Walker JM. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. *Life Sciences* 1995;56(23-24):2103-2109.

32. Matsuda LA, Bonner TI, Lolait SJ. Localization of cannabinoid receptor mRNA in rat brain. *Journal of Comparative Neurology* 1993;327:535-550.

33. Mechoulam R. The pharmacohistory of *Cannabis sativa*. In Mechoulam R, ed. *Cannabinoids as therapeutic agents*. Boca Raton, FL: CRC Press, 1986.

34. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. *Nature (London)* 1998;395(6700):381-383.

35. Moss DE, Johnson RL. Tonic analgesic effects of Δ^9-tetrahydrocannabinol as measured with the formalin test. *European Journal of Pharmacology* 1980;61(3):313-315.

36. Osborne PB, Vaughan CW, Wilson HI, Christie MJ. Opioid inhibition of rat periaqueductal grey neurones with identified projections to rostral ventromedial medulla in vitro. *Journal of Physiology* 1996;490(Pt 2):383-389.

37. Pan ZZ, Williams JT, Osborne PB. Opioid actions on single nucleus raphe magnus neurons from rat and guinea pig in vitro. *Journal of Physiology* 1990; 427:519-532.

38. Reche I, Fuentes JA, Ruiz-Gayo M. Potentiation of Δ^9-tetrahydrocannabinol-induced analgesia by morphine in mice: Involvement of mu- and kappa-opioid receptors. *European Journal of Pharmacology* 1996;318(7):11-16.

39. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB_1 receptors. *Pain* 1998;75(1): 111-119.

40. Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, et al. SR 141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Letters* 1994;350(2-3):240-244.

41. Rinaldi-Carmona M, Barth F, Millan J, Derocq JM, Casellas P, Congy C, Oustric D, Sarran M, Bouaboula M, Calandra B, et al. SR 144528, the first potent and selective antagonist of the CB_2 cannabinoid receptor. *Journal of Pharmacology and Experimental Therapeutics* 1998;284(2):644-650.

42. Smith FL, Cichewicz D, Martin ZL, Welch SP. The enhancement of morphine antinociception in mice by Δ^9-tetrahydrocannabinol. *Pharmacology, Biochemistry and Behavior* 1998;60(2):559-566.

43. Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Martin BR. The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. *Journal of Pharmacology and Experimental Therapeutics* 1994;270(1):219-227.

44. Sofia RD, Nalepa SD, Harakal JJ, Vassar HB. Anti-edema and analgesic properties of Δ^9-tetrahydrocannabinol (Δ^9-THC). *Journal of Pharmacology and Experimental Therapeutics* 1973;186(3):646-655.

45. Strangman NM, Patrick SL, Hohmann AG, Tsou K, Walker JM. Evidence for a role of endogenous cannabinoids in the modulation of acute and tonic pain sensitivity. *Brain Research* 1998;813(2):323-328.

46. Strangman NM, Walker JM. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. *Journal of Neurophysiology* 1999;82(1):472-477.

47. Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB_1 receptors in the rat central nervous system. *Neuroscience* 1998;83(2):393-411.

48. Vaughan CW, Connor MA, Bagley EE, Christie MJ. Actions of cannabinoids on membrane properties and synaptic transmission in rat periaqueductal grey neurons in vitro. *Molecular Pharmacology* 2000;57(2):288-295.

49. Vaughan CW, Ingram SL, Connor MA, Christie MJ. How opioids inhibit GABA-mediated neurotransmission. *Nature (London)* 1997;390(6660):611-614.

50. Vaughan CW, McGregor IS, Christie MJ. Cannabinoid receptor activation inhibits GABAergic neurotransmission in rostral ventromedial medulla neurons in vitro. *British Journal of Pharmacology* 1999;127(4):935-940.

51. Vivian JA, Kishioka S, Butelman ER, Broadbear J, Lee KO, Woods JH. Analgesic, respiratory and heart rate effects of cannabinoid and opioid agonists in rhesus monkeys: Antagonist effects of SR 141716A. *Journal of Pharmacology and Experimental Therapeutics* 1998;286(2):697-703.

52. Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96(21):1 2198-12203.

53. Welch SP, Stevens DL. Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine, in mice. *Journal of Pharmacology and Experimental Therapeutics* 1992;262(1):10-18.

54. Yaksh TL. The antinociceptive effects of intrathecally administered levonantradol and desacetyllevonantradol in the rat. *Journal of Clinical Pharmacology* 1981;21(8-9 supplement):334S-340S.

55. Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI. Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB_1 receptor knockout mice. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96(10):5780-5785.

Chapter 9

Cannabinoids As Neuroprotectants Against Ischemia

Aidan Hampson

INTRODUCTION

The brain is a high-energy usage tissue that requires a constant supply of glucose and oxygen, which is delivered by a system of blood vessels. Oxygen and glucose are required so that mitochondria can produce ATP, a major "currency" in the brain, used in almost all energy-requiring processes. A failure in the brain's energy supply rapidly induces a pathological state known as "ischemia."

When the brain is deprived of oxygen and glucose, a cascade of events begins that can rapidly result in substantial cell death. One early step in this cascade is the release of excitatory neurotransmitters such as glutamate,[14] which activate *N*-methyl *D*-aspartate (NMDA)-receptors and so induce a massive calcium entry into neurons.[4,9] This process is known as excitotoxicity, because cells literally *excite themselves to death*. Consequently, the uncontrolled influx of calcium indiscriminately activates gene expression and intracellular enzymes such as proteases.[18,20] Excitotoxicity also induces the production of lethal oxygen-free radicals such as superoxide and hydroperoxide.[16] These highly reactive oxidant species indiscriminately damage cell membranes and proteins and, if neurons survive that, oxidants also induce a program of delayed cell death (apoptosis). The exact processes by which toxic radicals are formed during ischemia are still being elucidated, but oxidants appear to be formed by stressed mitochondria, as they attempt to continue ATP production under conditions of limited oxygen and glucose availability.[1,6,7]

CANNABINOIDS AND ISCHEMIA

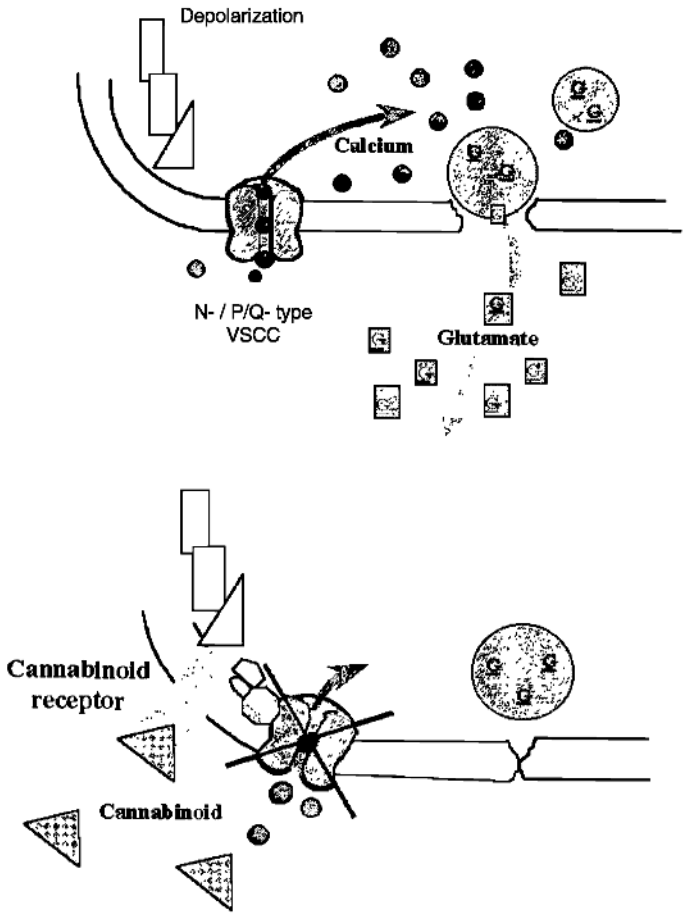
The idea of using cannabinoids to treat ischemia may initially seem surprising, and administration of *psychoactive* cannabinoids could certainly present problems as a treatment for cerebral ischemia. For example, an elderly and confused stroke patient would probably prefer not to take a drug that can further increase anxiety and confusion. Similarly, physicians would need to complete any neurological examination before administering psychoactive cannabinoids, since they affect motor coordination and other neurological responses. However, it should be remembered that cerebral ischemia is the third most common cause of death in adults in the developed world and current available treatment options are extremely limited and not without risk.[25]

The pathological process of ischemia begins as soon as oxygen and glucose supplies become limited, compromising the cell's ability to synthesize ATP. One of the primary functions of ATP in neurons is as an energy source for the pumps that maintain ion gradients across their cell membrane. Consequently, as ATP levels fall, the neuronal pumps are no longer able to prevent extracellular ions leaking in and neurons lose ability to maintain a membrane potential, a process known as depolarization. As the cell depolarizes, complete neurotransmitters release occurs, so that huge quantities of glutamate (an excitatory neurotransmitter) floods the affected area.

CANNABINOID RECEPTORS AND PRESYNAPTIC CALCIUM CHANNELS

Under normal circumstances, neurotransmitter release is controlled by a series of complex calcium-dependent mechanisms.[22] As neurons are electrically stimulated, the depolarization wave moves down the axon until it activates voltage sensitive calcium channels on presynaptic terminals. This depolarization wave activates N- and P/Q-type calcium channels, allowing entry of a small amount of calcium into the terminal and in turn, stimulating neurotransmitter release into the synaptic cleft. Although these calcium channels are voltage-activated, they are also regulated by G_i-protein coupled receptors, such as the cannabinoid receptor, CB_1.[27] Consequently, cannabinoids can inhibit neurotransmitter release[15,24] by activating CB_1 receptors on the presynaptic side of the cleft, which then inhibit the calcium channels that control neurotransmitter release. This role of cannabinoid receptors suggests that cannabinoids may be able to inhibit glutamate release during ischemia (see Figure 9.1). Cannabinoids have been demonstrated to prevent excitotoxicity in neuronal cultures where neurotransmitter release had been stimulated.[17] However, it is unclear whether cannabinoids would be similarly effective in vivo against hypoxia-induced neurotransmitter re-

FIGURE 9.1. Inhibition of Glutamate Release by Cannabinoids

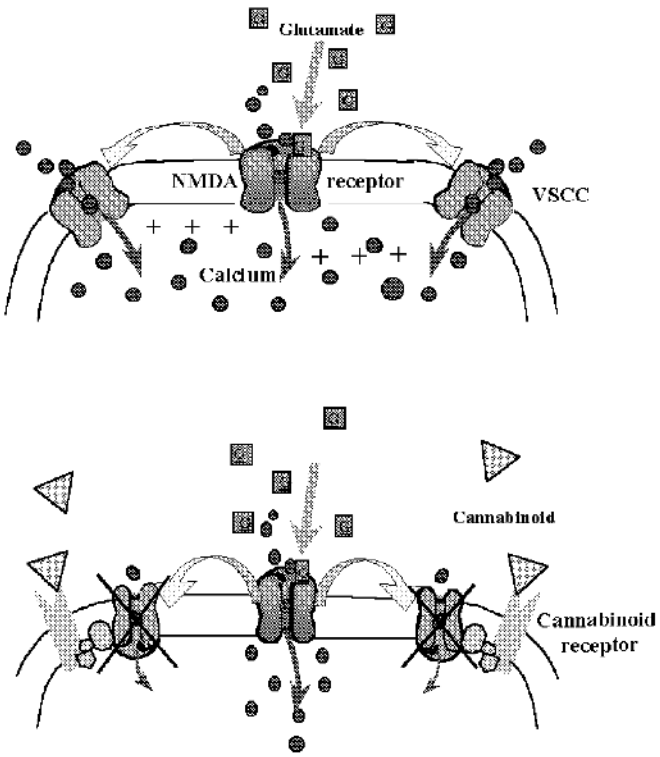


lease. It seems likely that ischemia would induce a much greater calcium influx than the mild conditions used in the in vitro study above, making voltage-sensitive calcium channels (and their regulators) redundant. In addition, for cannabinoid inhibition of presynaptic calcium channels to be effective as a therapy, they would probably need to be administered *before* ischemic onset-induced neurotransmitter release. Any attempt to inhibit neurotransmitter release after arrival at the hospital, and diagnosis and completion of neurological exams, may well be "too little-too late" for most patients. However, in some cases this may not be true. In many ischemia patients, glutamate is rapidly eliminated within minutes of its release, and the patient tends to stabilize and start to improve within hours of an attack. However, sometimes glutamate continues to be released for hours and days after ischemic onset,[8] a condition known as "progressive ischemia." In these cases, the patient's condition tends to worsen over time rather than stablize, and so cannabinoid administration may be a useful way of arresting neurotransmitter release and speed the patient's recovery.

CANNABINOID RECEPTORS AND POSTSYNAPTIC CALCIUM CHANNELS

For more than a decade, NMDA receptors have played a key role in mediating excitotoxic calcium influx.[4] However, it has recently been shown that while calcium entry is initiated by NMDA receptor activation, not all of the excitotoxic calcium flux actually enters neurons through this system.[11] During excitotoxicity, calcium flowing through NMDA receptors depolarizes that region of membrane and so activates nearby voltage-sensitive calcium channels (see Figure 9.2). These channels significantly contribute to the calcium load entering neurons during excitotoxic stimulation. In fact, approximately half of the calcium that flux into neurons during such events enters through postsynaptic N- and P/Q-type calcium channels.[11] A new study (in the author's lab) using isolated neuron preparations has reproduced this earlier finding confirming that 50 percent of the calcium excitotoxic entry flows through postsynaptic N- and P/Q-type calcium channels (manuscript in preparation). This new work also demonstrates (in vitro) that the ability of cannabinoids to inhibit calcium channels can prevent excitotoxicity in neurons. However, cannabinoid receptors only prevented about 20 percent

FIGURE 9.2. Inhibition of Glutamate-Induced Calcium Influx by Cannabinoids



of glutamate toxicity, perhaps because not all cortical neurons that are susceptible to glutamate also possess cannabinoid receptors.

A recent study in rats has also demonstrated that psychoactive cannabinoids can reduce brain injury caused by stroke.[17] The synthetic cannabinoid, WIN-55,212, was demonstrated to reduce stroke damage in rats by about 30 percent, using a cannabinoid receptor-dependent mechanism. Unfortunately, the cannabinoid was only protective when administered before or shortly after ischemic onset (a therapeutic window of 30 min before to 30 min after onset).

THE CANNABINOID SYSTEM AS AN ENDOGENOUS REGULATOR OF CALCIUM INFLUX

The ability of cannabinoid receptors to reduce excitotoxic damage in vitro may not only suggest their use as a treatment for ischemia, but also hints that excitotoxicity prevention may be a natural role for the endogenous cannabinoid system. Several studies have demonstrated that anandamide synthesis occurs in response to the rise in intracellular calcium levels which occurs when neurons are exposed to glutamate excitotoxicity.[3,13] In fact, even before cannabinoid receptors were discovered, fatty acid ethanolamides (such as anandamide), were known to be products formed in the brain during ischemia. Because cannabinoid receptor agonists can reduce glutamate-stimulated calcium entry, it is suggested that one role of the cannabinoid system is as a negative feedback mechanism which synthesizes endocannabinoids in response to excitotoxic calcium influx. When anandamide is released in response to rising calcium levels, it activates cannabinoid receptors, which serve to reduce further calcium influx through a voltage-sensitive calcium channel blockade. In this way the cannabinoid system serves to limit excitotoxicity. If this hypothesis is accurate, then cannabinoid administration to ischemia patients could help to enhance the activity of an endogenous neuroprotective system.

CANNABINOIDS AND NMDA RECEPTOR BLOCKADE

Ever since glutamate, NMDA receptors, and calcium were found to be involved in ischemia, NMDA receptor blockade has been a favored strategy for reducing ischemic damage. The NMDA receptor is a glutamate-activated ion channel, found in neuronal membranes which, upon activation, allows calcium ions to flux into the cell. Several studies and clinical trials over the past ten years have tried to reduce ischemic injury by blocking NMDA receptors.[19] Unfortunately, NMDA receptor blockade tends to induce significant side effects such as psychosis and cardiovascular problems.[5,21]

However, a nonpsychoactive cannabinoid called "dexanabinol" (HU-211) has been developed, which appears to act as an NMDA blocker, without inducing the side effects typical of these compounds (see Chapter 36). Dexanabinol has even been tried in a small clinical trial in young men with head injuries, where it clearly reduced the consequences of serious head injury. Although HU-211 was clearly beneficial soon after injury, the difference between treated and untreated groups was not visible six months after injury.[20] The reasons for this result are not completely clear, but suggest that traumatic head injury induces both immediate and long-term pathological processes, which are not yet completely understood.

OXIDANTS AND ISCHEMIA

One of the consequences of an excitotoxic inrush of calcium into neurons is the generation of oxidants such as hydrogen peroxide, peroxynitrite and hydroxide radicals. The free radicals produced in ischemic neurons wreak havoc inside cells both by oxidizing cell membranes, as well as damaging and activating nuclear factors that control delayed ischemic death (apoptosis). However, free radical damage can be arrested (at least experimentally) by increasing the amount of antioxidants available to "mop up" radicals.[2] Lipophilic antioxidants, in particular, show a great deal of promise in the treatment of ischemia. They tend to cross the blood-brain barrier well, they can neutralize free radicals in both cytosolic and membrane-delimited cell compartments, and, unlike water-soluble agents such as ascorbate, lipophiles are less likely to be made into dangerous radicals themselves by the action of ferric iron species.

CANNABINOIDS AS NEUROPROTECTIVE ANTIOXIDANTS

Cannabinoids can also prevent excitotoxicity without even interacting with cannabinoid receptors. Micromolar concentrations of both THC and cannabidiol (CBD, a nonpsychoactive cannabinoid) have been demonstrated to prevent neuronal excitotoxicity.[12] Although such concentrations of psychoactive cannabinoids are much too high for any therapeutic use, this observation of neuroprotection by CBD holds the promise of a cannabinoid therapy unrestricted by the psychomimetic complications typically associated with cannabinoids.

All classical cannabinoids and their synthetic equivalents contain a phenolic ring, which is similar to that found in antioxidants such as tocopherols (e.g., vitamin E) or butylated hydroxytoluene (BHT, a powerful antioxidant used to preserve foods). In a chemical antioxidant assay that depends on preventing oxidation of a dye, CBD, THC, and BHT were all excellent and indistinguishable in their antioxidant abilities.[10] Similarly, using a process

called "cyclic voltametry" to measure the "antioxidant power" of a molecule, CBD and BHT were equally powerful, as were other cannabinoids, including THC, dexanabinol, and nabilone (unpublished data). In in vitro models of neurotoxicity, cannabidiol, THC, and BHT were all demonstrated to be effective protectants with a comparable capacity to prevent neurotoxicity caused by either glutamate or direct addition of the oxidant "t"-butyl peroxide. Furthermore, in a head-to-head test of antioxidants, using a model of neuronal AMPA toxicity (a different glutamate toxicity model than that used previously), CBD and THC were shown to be significantly more protective than either of the commonly known antioxidant vitamins ascorbate (vitamin C) or α-tocopherol (vitamin E). However, in vitro antioxidant ability alone does not indicate whether a compound will be suitable as a neuroprotectant. Antioxidants can only be useful as prospective neuroprotectants so long as they can penetrate the blood-brain barrier without causing significant toxicity. Additionally, an antioxidant therapy needs to be given in a form that will not oxidize before it reaches its required site of action. Using these criteria, nonpsychoactive cannabinoids such as CBD appear to be better neuroprotective candidates than more common antioxidants. Cannabidiol is a more powerful antioxidant which protects better than tocopherol, and unlike BHT, CBD appears to have a low toxicity profile (BHT is a tumor promoter[26]). Both in animal trials and in two phase I clinical trials, CBD showed no toxicity, whether acutely administered (large dose, short duration[6]) or when given chronically.[7] Furthermore, unlike psychoactive cannabinoids, CBD does not impair motor coordination, cause vascular hypotension,[28] or induce anxiety (in fact, CBD is anxiolytic, see Chapter 33).[10]

At the present time, animal studies to investigate cannabidiol as a potential neuroprotectant are underway but have not yet concluded. Cannabidiol is being assessed in both a rat model of stroke and a higher mammal model of global ischemia.

In conclusion, although cannabinoid receptors may endogenously function as a safeguard against excitotoxicity, it is unclear whether cannabinoid receptor agonists will be useful as a therapy for ischemia. The concept of using such agents to arrest excitotoxicity is relatively new and all of the information required to accurately assess the usefulness of cannabinoids against ischemia is not yet available. One study has demonstrated that cannabinoids can protect in vivo, although the mechanism(s) by which this protection occurs have not been completely elucidated. However, the significant psychotropic side effects of cannabinoid receptor agonists will probably seriously restrict their use as anti-ischemic agents. On the other hand, nonpsychotropic cannabinoids such as dexanabinol and cannabidiol stand a much greater chance of entering the pharmacopeia.

REFERENCES

1. Anderson MF, Sims NR. Mitochondrial respiratory function and cell death in focal cerebral ischemia. *Journal of Neurochemistry* 1999;73(3):1189-1199.

2. Behl C. Vitamin E and other antioxidants in neuroprotection. *International Journal for Vitamin and Nutrition Research* 1999;69(3):213-219.

3. Cadas H, Gaillet S, Beltramo M, Venance L, Piomelli D. Biosynthesis of an endogenous cannabinoid precursor in neurons and its control by calcium and cAMP. *Journal of Neuroscience* 1996;16(12):3934-3942.

4. Choi DW, Koh JY, Peters SJ. Pharmacology of glutamate neurotoxicity in cortical cell culture: Attenuation by NMDA antagonists. *Neuroscience* 1988;8(1):185-196.

5. Christ G, Mundigler G, Merhaut C, Zehetgruber M, Kratochwill C, Heinz G, Siostrzonek P. Adverse cardiovascular effects of ketamine infusion in patients with catecholamine-dependent heart failure. *Anaesthesia and Intensive Care* 1997;25(3): 255-259.

6. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry and Behavior* 1991;40(3):701-708.

7. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980;21(3):175-185.

8. Davalos A, Castillo J, Serena J, Noya M. Duration of glutamate release after acute ischemic stroke. *Stroke* 1997;28(4):708-710.

9. Garthwaite G, Hajos F, Garthwaite J. Ionic requirements for neurotoxic effects of excitatory amino acid analogues in rat cerebellar slices. *Neuroscience* 1986;18(2):437-447.

10. Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology* 1990;100(4):558-559.

11. Hampson AJ, Bornheim LM, Scanziani M, Yost CS, Gray AT, Hansen BM, Leonoudakis DJ, Bickler P. Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission. *Journal of Neurochemistry* 1998;70(2):671-676.

12. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Δ^9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95(14):8268-8273.

13. Hansen HS, Moesgaard B, Hansen HH, Schousboe A, Petersen G. Formation of N-acyl-phosphatidylethanolamine and N- acetylethanolamine (including anandamide) during glutamate-induced neurotoxicity. *Lipids* 1999;34:327S-330S.

14. Jorgensen MB, Diemer NH. Selective neuron loss after cerebral ischemia in the rat: possible role of transmitter glutamate. *Acta Neurologica Scandinavica* 1982;66(5):536-546.

15. Katona I, Sperlagh B, Sik A, Kafalvi A, Vizi ES, Mackie K, Freund TFJ. Presynaptically located CB_1 cannabinoid receptors regulate GABA release from

axon terminals of specific hippocampal interneurons. *Neuroscience* 1999;19(11): 4544-4558.

16. Murphy AN, Fiskum G, Beal MF. Mitochondria in neurodegeneration: Bioenergetic function in cell life and death. *Journal of Cerebral Blood Flow and Metabolism* 1999;19(3):231-245.

17. Nagayama T, Sinor AD, Simon RP, Chen J, Graham SH, Jin K, Greenberg DA. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. *Journal of Neuroscience* 1999;19(8):2987-2995.

18. Orrenius S, Nicotera P. The calcium ion and cell death. *Journal of Neural Transmission. Supplementum* 1994;43:1-11.

19. Ozyurt E, Graham DI, Woodruff GN, McCulloch J. Protective effect of the glutamate antagonist MK-801 in focal cerebral ischemia in the cat. *Journal of Cerebral Blood Flow and Metabolism* 1988;8(7):138-143.

20. Pharmos Announces Successful Phase II Head Trauma Study. Marijuana analog benefits brain injured patients (Pharmos Corp press release), October 1998.

21. Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: Relationship to steady-state plasma concentrations. *Anesthesiology* 1998;88:82-88.

22. Schanne FA, Kane AB, Young EE, Farber JL. Calcium dependence of toxic cell death: A final common pathway. *Science* 1979;9206(4419):700-702.

23. Shen M, Thayer SA. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. *Molecular Pharmacology* 1998;54(3): 459-462.

24. Sullivan JM. Mechanisms of cannabinoid-receptor-mediated inhibition of synaptic transmission in cultured hippocampal pyramidal neurons. *Journal of Neurophysiology* 1999;82(3):1286-1294.

25. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *New England Journal of Medicine* 1995;333(24):1581-1587.

26. Thompson JA, Bolton JL, Malkinson AM. Relationship between the metabolism of butylated hydroxytoluene (BHT) and lung tumor promotion in mice. *Experimental Lung Research* 1991;17(2):439-453.

27. Twitchell W, Brown S, Mackie K. Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. *Journal of Neurophysiology* 1997;78(1):43-50.

28. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta-9-THC in normal subjects. *Psychopharmacology* 1982;76(3):245-250.

Chapter 10

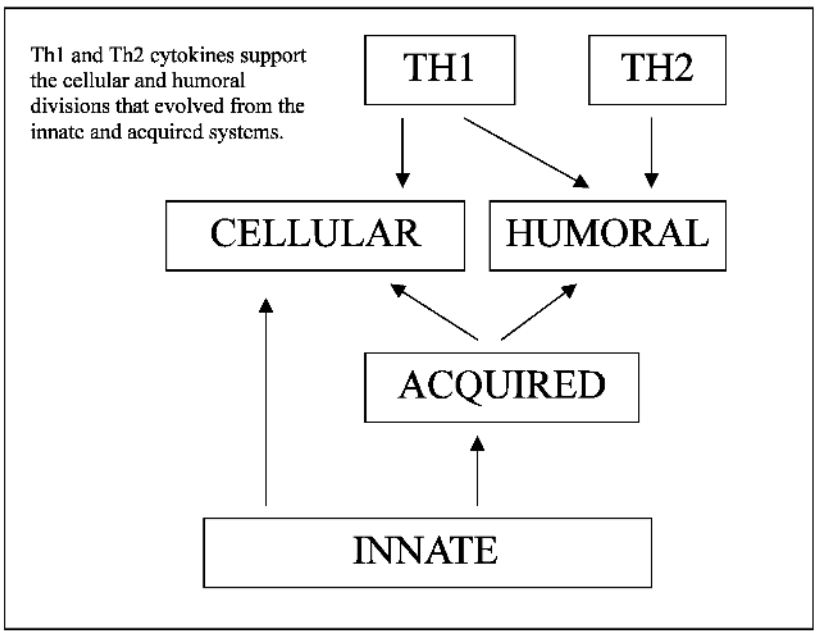
Possible Mechanisms in Autoimmune Diseases

Robert Melamede

Historically, immune responses have been classified by either of two well-known schemes. In one, there is the innate and the acquired response. In the other, there is the cell-mediated and humoral response categories. There is overlap between these schemes. To understand the pivotal role that the cannabinoid receptor circuit plays in modulating the immune system, and to understand potential therapeutic applications of cannabinoids, a more modern division into T-helper 1 (Th1) and T-helper 2 (Th2) responses must be made (see Figure 10.1).

The distinction between Th1 and Th2 is best made by examining the cytokine profile associated with a given response. All immune responses are controlled by chemical messengers known as cytokines. Cytokines are proteins that support, or inhibit, the replication and function of specific cell types. Cytokines are released and controlled by immunologically responsive cells. They also control cells that have receptors for a specific cytokine. There are characteristic cytokine profiles that correspond to each type of immune response. Specifically, the Th1 response is characterized by higher levels of the proinflammatory cytokines IL1, IL2, IL12, and IL18 and gamma interferon,[8] whereas IL4, IL10, and IL13 dominate a Th2 response.[7] There are diseases and conditions where one, and not the other, of the two immune responses is most beneficial for an organism. Conversely, the inappropriate response may be detrimental to health. For example, successful defense against parasitic infections typically requires the production of large amounts of the free radical NO that occurs with a Th1-dominated immune response. However, excesses of this free radical are implicated as a causative agent for autoimmune diseases.[23] In general, inflammation and free radicals play an important defensive role in Th1 responses. In contrast, the Th2 response minimizes both of these Th1 characteristics. Delta-9-

FIGURE 10.1. Th1 and Th2 Cytokine Responses



tetrahydrocannabinol (THC) enters into the picture because it and other cannabinoids inhibit the Th1 response and promote a Th2 response.[18,27]

From an evolutionary standpoint, the innate immune response is more primitive in that its appearance predates the development of the acquired immune response. In a simplistic sense, it can in part be viewed as having been built upon natural free radical-producing mechanisms. The ability to focus these chemically reactive species on foreign invaders serves as a protective mechanism. It should be kept in mind that free radicals are an unavoidable consequence of oxidative metabolism. The danger of using a free radical-based defensive system is in the limits of its targeting accuracy. Free radicals are highly reactive and affect all the macromolecular components of cells. A localized inflammatory response exposes nontarget tissue to increased levels of free radicals that are intrinsically mutagenic. The wrong mutations can turn a helpful immune response against normal tissue and thus create an autoimmune disease.

The reported therapeutic value of cannabinoids in the treatment of some autoimmune diseases probably lies in its ability to inhibit the Th1 response and its associated free radical production. Marijuana and its main psychoactive component, THC, have been shown to exert a complex, often seemingly contradictory, pattern of immune alterations including both stimulatory and inhibitory effects (see Chapter 25) that are further complicated by age and dose-dependent considerations. However, many of these apparent contradictions can be resolved by considering the nature of immune deviation as determined by the Th1 versus Th2 cytokine profile in

the experimental or clinical situation under examination. The Th1 cytokine profile supports B-cells producing antibodies of the IgG1 and IgG3 isotypes in humans,[1] whereas Th2 cytokine-driven antibody production is characterized by the IgG2 isotypes. Autoimmune diseases can be either Th1 or Th2 dominated. Those that are driven by a Th1 type of response may well benefit from therapies that stimulate the CB receptors and promote Th2 deviation.

Many autoimmune diseases seem to be Th1-dominated.[36] For example, multiple sclerosis, arthritis, type 1 diabetes (insulin-dependent diabetes mellitus, IDDM), and Crohn's disease usually seem to be mediated by Th1-supported cells. In contrast, systemic sclerosis and Grave's disease are examples of diseases that seem to be Th2-dominated. Systemic lupus erythematosus (SLE) does not nicely fit into either of these two categories since some individuals appear to be Th1-deviated and others Th2-deviated. Because marijuana and THC deviate the immune system towards a Th2 response, in addition to the demonstrated pain relieving properties of THC (see Chapters 8 and 15), this cannabinoid may partially correct the basic immunological imbalance that underlies the symptoms of some of these diseases.

Support for actual mechanistic benefits to therapeutic cannabis may be drawn directly, and by inference, from the scientific literature using both human and animal models. Despite limitations, this nonclinical approach must be taken until more clinical data are generated. However, parallels may be drawn between therapies that appear to have the same underlying mode of action as would be expected to result from the activation of cannabis receptors. For example, the immune-modulating drug linomide, which causes a Th2 immune deviation,[17] has been shown in experimental autoimmune encephalomyelitis (EAE), an animal model for the demyelinating disease multiple sclerosis (MS), to block both the clinical and histological signs of the disease.[22] Complementarily, the antioxidant N-acetyl-L-cysteine (NAC), a potent free radical scavenger, prevents EAE.[21] Similarly, 95 percent of mice treated with THC after treatment to induce EAE survived, whereas 98 percent of the mice that received no THC died.[24] A similar effect has been observed after treatment with Δ^8-THC.[44] Thus, it appears that there is sound scientific support for the use of cannabinoids as therapeutic agents in the treatment of MS as suggested by anecdotal reports.

Crohn's disease, characterized by intestinal inflammation, is another example of a Th1-mediated disease. Anecdotal reports of beneficial marijuana use for this disease gain support by examining modern pharmaceutical approaches. Downregulation of Th1 effectors has produced dramatic results in the treatment of this disease. New immuno-therapeutic strategies that treat Crohn's disease with antitumor necrosis factor (TNFα) antibodies, have induced complete remissions and few side effects.[19,39] THC has been shown

to inhibit TNFα (see Chapter 25). Thus, the same therapeutic targets of the newest pharmaceuticals are acted upon by one of nature's oldest medicines.

Psoriasis, characterized by scaly patches of dry and often cracking skin, shares the cell proliferation characteristic of rheumatoid arthritis (RA) and also appears to be mediated by Th1 cytokines.[14] Skin lesions are infiltrated with T-cells that secrete Th1 cytokines.[37] The etiology of the T-cell pathology is indicated by the specific response of Th1 T-cells to peptides sharing homology between group A beta-hemolytic streptococcal proteins and keratin.[35] Thus, gamma interferon is elevated in psoriatic plaques, and although it normally would be expected to have an antiproliferative effect on keratinocytes, gamma interferon does not appear to do so in psoriasis.[16] High levels of TNFα appear to correlate with disease severity.[25] Other pro-inflammatory cytokines characteristic of a Th1 response, such as IL6,[28] IL8,[5] and IL12,[45] have also been associated with psoriasis. Therapeutic agents that shift the psoriatic cytokine environment away from Th1, and/or to that of a Th2 response, have been used for psoriasis treatment. Dimethylfumerate, which inhibits IL6,[28,34] and the Th2 cytokine IL10 have been used therapeutically with some success in the treatment of psoriasis.[3,4] Thus, a THC-induced immunological deviation to a Th2 response would be expected to benefit psoriasis patents. It is worth noting that higher levels of free radicals have been associated with psoriasis. In particular after PUVA treatment (a combination of psoralen and long-wave ultraviolet radiation), antioxidant inhibitable clastogenic factors have been found that are probably responsible for phototherapy-associated cancers.[9] Cannabinoids have been shown to have strong antioxidant properties (see Chapter 9) which may be related to their anticancer properties.[11,13,31]

In both rheumatoid arthritis (RA) and SLE, abundant data link these diseases with Th1-supported immune imbalances. Both diseases are more prevalent in females and are strongly linked with age and hormone status.[29] With RA the autoimmunity results in chronic inflammation and cartilage destruction. The Th1 nature of RA is demonstrated by the fact that 75 percent of patients improve during pregnancy[29] when Th2 responses dominate. In addition, the Th2 cytokine, interleukin 4, has been used successfully in the treatment of RA.[40] Also, a Th1 immunological deviation has been strongly associated with reactive arthritis such as is induced by bacterial infection.[12] It therefore seems that the combination of marijuana's pain relieving, anti-inflammatory, and Th2 deviating properties would support the anecdotal reports of its successful use for arthritic conditions.

The immune deviation pattern found with SLE is more complex than what is observed with RA. Depending on age and hormone status at time of onset[43] SLE may show a Th1 or a Th2 cytokine profile. Again, anecdotal reports and experimental data indicate that THC could have beneficial effects on this disease when used appropriately.

Simplistically, SLE is considered to be a B-cell mediated disease since it is characterized by abnormal antiself antibodies; it might be expected that THC would be harmful to SLE patients. However, it should be remembered that depending on the isotype of the antibodies produced, the B-cells may be supported by either Th1[26] or a Th2 cytokines.[15] In general, it might be expected that when lupus occurs early in life, especially when associated with pregnancy, it may be expected to be supported by Th2 cytokines[43] and cannabinoid use would be contraindicated. In contrast, women who develop SLE postpartum or postmenopause might be expected to have a Th1-mediated disease that could benefit from cannabinoid based therapeutics.

One can speculate that cannabinoids may also have a beneficial effect on SLE by a hormonal regulatory mechanism. THC has been shown to reduce prolactin levels in mice[42] and the CB_1 receptor has been found in the anterior pituitary gland. SLE has an associated hyperprolactinemia.[6] Some studies suggest that elevated prolactin levels may be associated with disease severity. The reduction of prolactin appears to reduce disease symptoms.[41] It is likely that SLE represents a disease that results from numerous possible molecular and biochemical imbalances. Depending on the idiosyncrasies of an individual SLE patient, THC may be helpful or harmful. Hopefully, future research will extend these observations from mice to humans, allowing for appropriately tailored therapies.

IDDM is typically considered to be CD4+, Th1-mediated autoimmune disease[30] that results from the apoptosis of the insulin-producing pancreatic beta cells. However, as may be seen in other autoimmune diseases there may be indications of both Th1 and Th2 causative agents.[2] Using nonobese diabetic mice (NOD mice), there are numerous studies that demonstrate the role of immune deviation in this disease. When this disease first develops, islet-infiltrating T-cells display a Th1 cytokine profile. However, in mice that merely develop insulitis without beta cell destruction, the T-cells express the Th2 cytokine IL4.[10] Similarly, potent antidiabetic effects were produced by immune deviation to a Th2 profile that was accomplished by treating prediabetic mice with IL10/FC therapy.[46] In support of anecdotal observations by diabetics using THC, it should also be noted that THC stimulates glucose metabolism[32] in human glioma cells in tissue culture, in mice,[33] and promotes insulin release from rat islet cells.[20]

In conclusion, cannabinoids constitute an important class of immune modulators. Their ability to promote a Th2 immune deviation can be of benefit for a large group of people who suffer from diseases that are due to inappropriate Th1 responses. The general apparent safety of this class of drugs,[38] relative to most prescription drugs that are routinely used, suggests that they should be made readily available to those who can benefit from their use.

REFERENCES

1. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996;383(6603):787-793.

2. Almawi WY, Tamim H, Azar ST. Clinical review 103: T helper type 1 and 2 cytokines mediate the onset and progression of type I (insulin-dependent) diabetes. *Journal of Clinical Endocrinology and Metabolism* 1999;84(5):1497-1502.

3. Asadullah K, Docke WD, Ebeling M, Friedrich M, Belbe G, Audring H, Volk HD, and Sterry W. Interleukin 10 treatment of psoriasis: Clinical results of a phase 2 trial. *Archives of Dermatology* 1999;135(2):187-192.

4. Asadullah K, Sterry W, Stephanek K, et al. IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. *Journal of Clinical Investigation* 1998;101(4):783-794.

5. Biasi D, Carletto A, Caramaschi P. Neutrophil functions and IL-8 in psoriatic arthritis and in cutaneous psoriasis. *Inflammation* 1998;22(5):533-543.

6. Blanco-Favela F, Quintal-Alvarez G, Leanos-Miranda A. Association between prolactin and disease activity in systemic lupus erythematosus. Influence of statistical power. *Journal of Rheumatology* 1999;26(1):55-59.

7. De Carli M, D'Elios MM, Zancuoghi G, Romagnani S, Del Prete G. Human Th1 and Th2 cells: Functional properties, regulation of development and role in autoimmunity. *Autoimmunity* 1994;18(4):301-308.

8. Dinarello CA. Role of pro- and anti-inflammatory cytokines during inflammation: Experimental and clinical findings. *Journal of Biological Regulators and Homeostatic Agents* 1997;11(3):91-103.

9. Filipe P, Emerit I, Alaoui Youssefi A, Levy A, Cernjavski L, Freitas J, and deCastro JL. Oxyradical-mediated clastogenic plasma factors in psoriasis: Increase in clastogenic activity after PUVA. *Photochemistry and Photobiology* 1997;66(4): 497-501.

10. Fox CJ, Danska JS. IL-4 expression at the onset of islet inflammation predicts nondestructive insulitis in nonobese diabetic mice. *Journal of Immunology* 1997; 158(5):2414-2424.

11. Harris LS. Analgesic and antitumor potential of the cannabinoids. In Cohen S, Stillman RC, eds. *The Therapeutic potential of marihuana*. New York: Plenum Medical Book, 1976, pp. 299-312.

12. Hermann E. T cells in reactive arthritis. *APMIS* 1993;101(3):177-186.

13. Holly EA, Lele C, Bracci PM, McGrath MS. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *American Journal of Epidemiology* 1999;150(4):375-389.

14. Horrocks C, Holder JE, Berth-Jones J, Camp RD. Antigen-independent expansion of T cells from psoriatic skin lesions: Phenotypic characterization and antigen reactivity. *British Journal of Dermatology* 1997;137(3):331-338.

15. Ishida H. [Clinical implication of IL-10 in patients with immune and inflammatory diseases]. *Rinsho Byori* 1994;42(8):843-852.

16. Jackson M, Howie SE, Weller R, Sabin E, Hunter JA, McKenzie RC. Psoriatic keratinocytes show reduced IRF-1 and STAT-1alpha activation in response to gamma-IFN. *FASEB Journal* 1999;13(3):495-502.

17. Karussis D, Abramsky O, Rosenthal Y, Mizrachi-Koll R, Ovadia H. Linomide downregulates autoimmunity through induction of Th2 cytokine production by lymphocytes [In Process Citation]. *Immunology Letters* 1999;67(3):203-208.

18. Klein TW, Newton C, Friedman H. Cannabinoid receptors and the cytokine network. *Advances in Experimental Medicine and Biology* 1998;437:215-222.

19. Kmiec Z. Cytokines in inflammatory bowel disease. *Archivum Immunologiae et therapiae Experimentalis* 1998;46(3):143-155.

20. Laychock SG, Hoffman JM, Meisel E, Bilgin S. Pancreatic islet arachidonic acid turnover and metabolism and insulin release in response to delta-9-tetrahydrocannabinol. *Biochemical Pharmacology* 1986;35(12):2003-2008.

21. Lehmann D, Karussis D, Misrachi-Koll R, Shezen E, Ovadia H, Abramsky O. Oral administration of the oxidant-scavenger N-acetyl-L-cysteine inhibits acute experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 1994; 50(1):35-42.

22. Lehmann D, Karussis D, Mizrachi-Koll R, Linde AS, Abramsky O. Inhibition of the progression of multiple sclerosis by linomide is associated with upregulation of CD4+/CD45RA+ cells and downregulation of CD4+/CD45RO+ cells. *Clinical Immunology and Immunopathology* 1997;85(2):202-209.

23. Liew FY. Nitric oxide in infectious and autoimmune diseases. *Ciba Foundation Symposium* 1995;195:234-239.

24. Lyman WD, Sonett JR, Brosnan CF, Elkin R, Bornstein MB. Δ^9-tetrahydrocannabinol: A novel treatment for experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 1989;23(1):73-81.

25. Mussi A, Bonifati C, Carducci M, D'Agosto G, Pimpinelli F, D'Urso D, D'Auria L, Fazio M, and Ameglio F. Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis. *Journal of Biological Regulators and Homeostatic Agents* 1997;11(3):115-118.

26. Nakajima A, Hirose S, Yagita H, Okumura K. Roles of IL-4 and IL-12 in the development of lupus in NZB/W F1 mice. *Journal of Immunology* 1997;158(3):1466-1472.

27. Newton C, Klein T, Friedman H. The role of macrophages in THC-induced alteration of the cytokine network. *Advances in Experimental Medicine and Biology* 1998;437:207-214.

28. Ockenfels HM, Schultewolter T, Ockenfels G, Funk R, Goos M. The antipsoriatic agent dimethylfumarate immunomodulates T-cell cytokine secretion and inhibits cytokines of the psoriatic cytokine network. *British Journal of Dermatology* 1998;139(3):390-395.

29. Ostensen M. Sex hormones and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. *Annals of the New York Academy of Sciences* 1999;876: 131-143, discussion 144.

30. Rapoport MJ, Mor A, Vardi P, Ramot Y, Winkler R, Hindi A, and Bistritzer T. Decreased secretion of Th2 cytokines precedes Up-regulated and delayed secretion of Th1 cytokines in activated peripheral blood mononuclear cells from patients with insulin-dependent diabetes mellitus. *Journal of Autoimmunity* 1998;11(6): 635-642.

31. Sanchez C, Galve-Roperh I, Canova C, Brachet P, Guzman M. Δ^9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. *FEBS Letters* 1998; 436(1):6-10.

32. Sanchez C, Velasco G, Guzman M. Δ^9-tetrahydrocannabinol stimulates glucose utilization in C6 glioma cells. *Brain Research* 1997;767(1):64-71.

33. Sanchez C, Velasco G, Guzman M. Metabolic stimulation of mouse spleen lymphocytes by low doses of Δ^9-tetrahydrocannabinol. *Life Sciences* 1997;60(19): 1709-1717.

34. Sebok B, Bonnekoh B, Vetter R, Schneider I, Gollnick H, Mahrle G. The antipsoriatic dimethyl-fumarate suppresses interferon-gamma-induced ICAM-1 and HLA-DR expression on hyperproliferative keratinocytes. Quantification by a culture plate-directed APAAP-ELISA technique. *European Journal of Dermatology* 1998;8(1):29-32.

35. Sigmundsdottir H, Sigurgeirsson B, Troye-Blomberg M, Good MF, Valdimarsson H, Jonsdottir I. Circulating T cells of patients with active psoriasis respond to streptococcal M-peptides sharing sequences with human epidermal keratins. *Scandinavian Journal of Immunology* 1997;45(6):688-697.

36. Singh VK, Mehrotra S, Agarwal SS. The paradigm of Th1 and Th2 cytokines: Its relevance to autoimmunity and allergy. *Immunologic Research* 1999; 20(2): 147-161.

37. Szabo SK, Hammerberg C, Yoshida Y, Bata-Csorgo Z, Cooper KD. Identification and quantitation of interferon-gamma producing T cells in psoriatic lesions: Localization to both CD4+ and CD8+ subsets. *Journal of Investigative Dermatology* 1998;111(6):1072-1078.

38. Taylor HG. Analysis of the medical use of marijuana and its societal implications. *Journal of the American Pharmaceutical Association* 1998;38(2):220-227.

39. van Montfrans C, Camoglio L, van Deventer SJ. Immunotherapy of Crohn's disease. *Mediators of Inflammation* 1998;7(3):149-152.

40. van Roon JA, van Roy JL, Duits A, Lafeber FP, Bijlsma JW. Proinflammatory cytokine production and cartilage damage due to rheumatoid synovial T helper-1 activation is inhibited by interleukin-4. *Annals of the Rheumatic Diseases* 1995;54(10):836-40.

41. Walker SE, McMurray RW, Houri JM, Allen SH, Keisler D, Sharp GC, and Schlechte JA. Effects of prolactin in stimulating disease activity in systemic lupus erythematosus. *Annals of the New York Academy of Sciences* 1998;840:762-772.

42. Wenger T, Toth BE, Juaneda C, Leonardelli J, Tramu G. The effects of cannabinoids on the regulation of reproduction. *Life Sciences* 1999;65(6-7):695-701.

43. Wilder RL. Hormones, pregnancy, and autoimmune diseases. *Annals of the New York Academy of Sciences* 1998;840:45-50.

44. Wirguin I, Mechoulam R, Breuer A, Schezen E, Weidenfeld J, Brenner T. Suppression of experimental autoimmune encephalomyelitis by cannabinoids. *Immunopharmacology* 1994;28(3):209-214.

45. Yawalkar N, Karlen S, Hunger R, Brand CU, Braathen LR. Expression of interleukin-12 is increased in psoriatic skin. *Journal of Investigative Dermatology* 1998;111(6):1053-1057.

46. Zheng XX, Steele AW, Hancock WW, Stevens AC, Nickerson PW, Roy-Chaudhury P, Tian Y, and Strom TB. A noncytolytic IL-10/Fc fusion protein prevents diabetes, blocks autoimmunity, and promotes suppressor phenomena in NOD mice. *Journal of Immunology* 1997;158(9):4507-4513.

PART III:
INDICATIONS FOR CANNABIS
AND THC

Chapter 11

Review of Therapeutic Effects

Franjo Grotenhermen

Cannabis preparations have been employed in the treatment of numerous diseases, with marked differences in the available supporting data (see Table 11.1). For applications such as nausea and vomiting associated with cancer chemotherapy, anorexia and cachexia in HIV/AIDS, and spasticity in multiple sclerosis and spinal cord injury, there is strong evidence for medical benefits. For indications such as epilepsy, movement disorders, and depression, much less data is available. However, the history of clinical use of cannabis and cannabinoids has demonstrated that the scientific evidence for a specific indication does not implicitly reflect the actual therapeutic potential for a given disease.

Clinical studies with single cannabinoids, or, less often, with whole plant preparations (smoked marijuana, encapsulated cannabis extract), have often been inspired by positive anecdotal experiences of patients employing

TABLE 11.1. Possible Indications for Dronabinol and Cannabis

• Allergy, pruritus
• Anorexia and cachexia
• Asthma
• Dependency and withdrawal
• Depression, bipolar disorders, and anxiety disorders
• Epilepsy
• Glaucoma
• Inflammation and infection
• Movement disorders
• Nausea and vomiting
• Painful conditions and pain syndromes
• Spasticity

crude cannabis products (usually without legal sanction). The antiemetic,[7] appetite enhancing,[22] relaxing effects,[4] analgesia,[20] and therapeutic use in Tourette's syndrome were all discovered or rediscovered in this manner.

Incidental observations have also revealed therapeutically useful effects. This occurred in a study conducted by Volicer and colleagues[26] in patients with Alzheimer's disease in which the primary issue was an examination of the appetite-stimulating effects of Δ^9-THC. Not only appetite and body weight increased, but disturbed behavior among the patients also decreased following the intake of the verum drug.[26] The discovery of decreased intraocular pressure with THC administration in the beginning of the 1970s was also serendipitous (see Chapter 19). Additional interesting indications that have not been scientifically investigated, but remain common problems in modern medicine, may benefit from treatment with cannabis or cannabinoids. For this reason, surveys have been conducted in the past three to four years questioning individuals who use cannabis therapeutically. These surveys were conducted either as oral nonstandardized interviews in the course of investigations of state or scientific institutions (House of Lords Select Committee on Science and Technology in the United Kingdom, Institute of Medicine in the United States) on the therapeutic potential of cannabis,[12,13] or as anonymous surveys using standardized questionnaires.[2,5,6,18,23,25]

HIERARCHY OF THERAPEUTIC EFFECTS

To do justice to the scientific evidence with regard to different indications, a hierarchy of therapeutic effects can be devised.

In this overview no distinction will be made between isolated THC (dronabinol) and natural cannabis products. Indications for THC will be regarded as indications for cannabis and vice versa. (For more information, see the various reviews on indications.[1,3,8,9,10,13,15,16])

1. *Established effect:** nausea and vomiting, anorexia, and weight loss.
2. *Relatively well-confirmed effect:* spasticity, painful conditions, especially neurogenic pain, movement disorders, asthma, glaucoma.
3. *Less confirmed effect:* allergies, inflammation, infection, epilepsy, depression, bipolar disorders, anxiety disorders, dependency and withdrawal.

---

*The only approved preparations to date, Marinol (dronabinol, Δ^9-THC) and Cesamet (nabilone), are approved for the indication of nausea and vomiting associated with cancer chemotherapy. Marinol is also approved for anorexia and cachexia in HIV/AIDS.

4. *Basic research stage:* autoimmune diseases (see Chapter 10), cancer (see Chapters 5 and 35), neuroprotection (see Chapters 9 and 36), fever, disorders of blood pressure.

This hierarchy may not necessarily reflect the actual clinical benefit derived by patients employing cannabinoid treatments. Additional research will likely result in new correlations. For example, benefit of cannabis in movements disorders would have to be classified as a less confirmed effect only a short time ago. Recent controlled clinical investigations of THC in Tourette's syndrome give hope that cannabis and cannabinoids may eventually be regarded as established indications in this disorder within a few years (see Chapter 18). Results of a clinical study at the Medical School of Hannover, Germany, examining the use of cannabis products spread quickly in self-help organizations in the German language area in Europe, and the benefit of cannabis in this disease is now well known by many patients. Anecdotes as to the efficacy of cannabis/THC in indications that have not been confirmed in controlled studies must be judged with caution.

INDICATIONS

Spasticity

(See Chapter 17.)

In small clinical trials of Δ^9-tetrahydrocannabinol, nabilone, and cannabis, a beneficial effect on spasticity caused by multiple sclerosis or spinal cord injury has been observed (see Figure 11.1). Among other positively influenced symptoms were pain, paraesthesia, tremor, and ataxia. In folk medicine there are reports of improved bowel and bladder control.[5] Some anecdotal evidence of a benefit of marijuana in spasticity due to central lesions also exists.

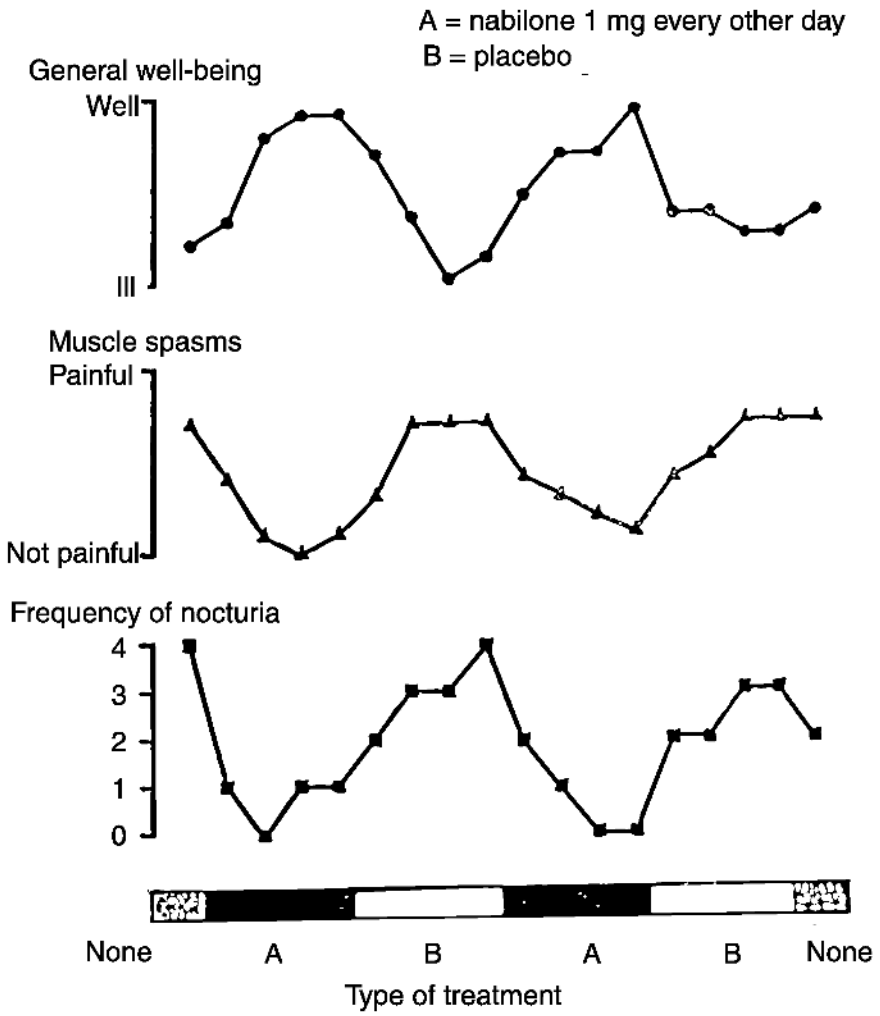
Movement Disorders

(See Chapter 18.)

There are some positive anecdotal reports of therapeutic response to cannabis in Tourette's syndrome, dystonia, and tardive dyskinesia. The use in Tourette's syndrome is currently being investigated in clinical studies. Many patients achieve a modest improvement, however some show a considerable response or even complete symptom control.

Cannabidiol in dosages between 100 and 600 mg per day produced improvements of 20 to 50 percent in five patients with dystonia. In MS patients, benefits on ataxia and reduction of tremor have been observed following the administration of THC (see Chapter 17) (see Figures 11.2 and 11.3). Despite

FIGURE 11.1. Influence of Therapy with Nabilone on General Well-Being, Spasticity, and Nocturia in an MS Patient Receiving Alternating Nabilone and Placebo



Source: Martyn CN, Illis LS, Thom J. Nabilone in the treatment of multiple sclerosis. *Lancet* 1995;345(8949):579. Reprinted with permission. © by The Lancet Ltd.

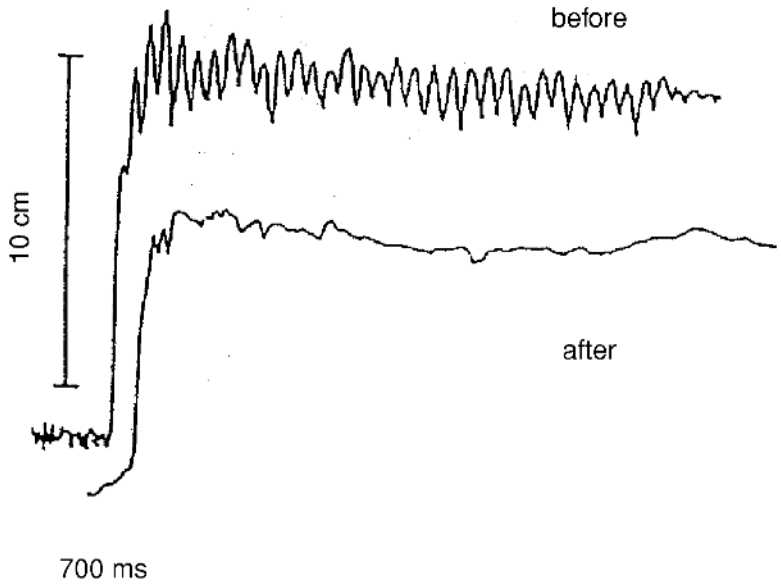
occasional positive reports, no objective success has been found in parkinsonism or Huntington's disease. However, cannabis products may prove useful in levodopa-induced dyskinesia in Parkinson's disease without worsening the primary symptoms (see Chapter 18).

Pain

(See Chapters 8, 15, and 16.)

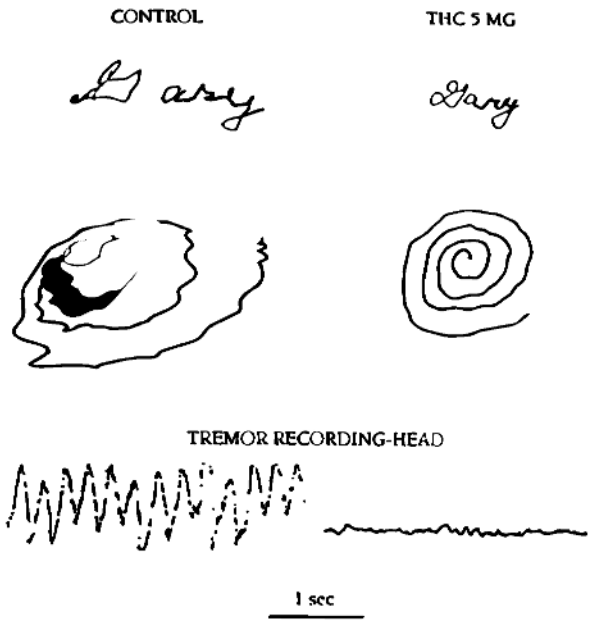
Few clinical studies of cannabinoids in painful conditions exist. In two trials, oral THC proved to be effective against cancer pain in doses of 15 and

FIGURE 11.2. Electromagnetic Recording of the Finger and Hand Action Tremor in an MS Patient Before and After Smoking a Marijuana Cigarette



Source: Meinck HM, Schönle PWA, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology* 1989;236(2): 120-122. Reprinted with permission.

FIGURE 11.3. Handwriting Sample and Movement Artifact from the Head of an MS Patient Before and 90 min After Ingestion of 5 mg THC



Source: Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology* 1983;13(6):669-671. © 1983. Reprinted by permission of John Wiley & Sons, Inc.

20 mg, respectively. However, some patients experienced intolerable side effects. In a single case double-blind study a patient with familial Mediterranean fever clearly reduced his need for opiates while receiving THC (50 mg per day divided in five doses) in comparison to placebo.

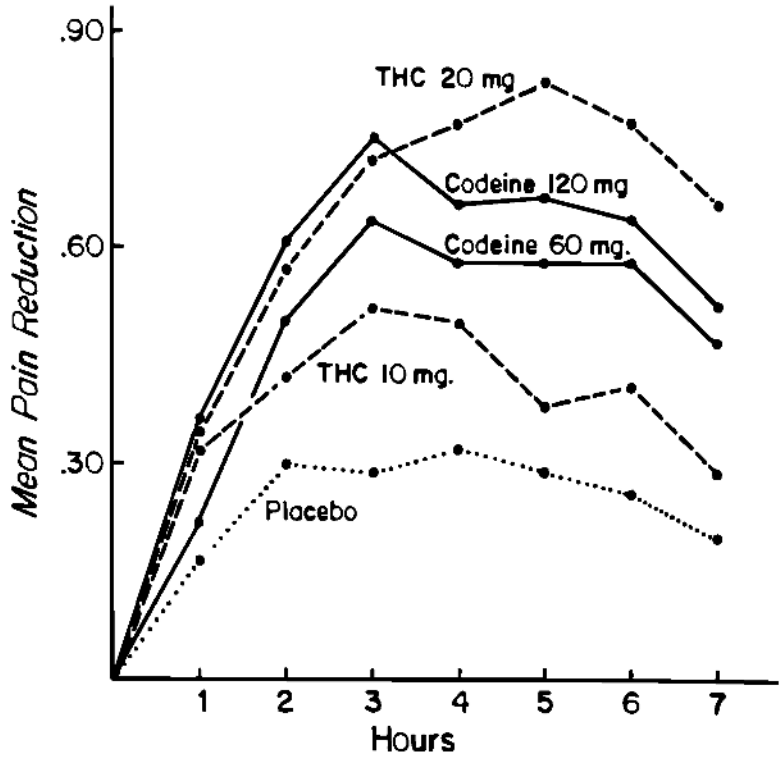
According to reports from pain therapists, the simultaneous administration of opiates and cannabis appears to be promising, particulary since cannabis does not cause respiratory depression. Cannabis has been successfully used in modern folk medicine in a multitude of painful conditions, among them migraine and other forms of headaches, musculoskeletal disorders, arthritis, neuralgias, neuropathy, dysmenorrhea, ulcerative colitis, Crohn's disease, etc. (see Figure 11.4).

Anorexia and Cachexia

(See Chapter 13.)

An appetite-enhancing effect of THC is observed with daily divided doses totalling 5 mg. When required, the daily dose may be increased to 20

FIGURE 11.4. Mean Hourly Pain Reduction with THC, Codeine and Placebo in Patients with Cancer Pain



Source: Noyes R, Brunk ST, Avery DH, Canter A. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics* 1975;18(1):84-89. Reprinted with permission by Clinical Pharmacology and Therapeutics.

mg. In a long-term study of 94 AIDS patients, the appetite-stimulating effect of THC continued for months, confirming the appetite enhancement noted in a shorter six-week study. THC doubled appetite on a visual analogue scale in comparison to placebo. Patients tended to retain a stable body weight over the course of seven months.

A positive influence on body weight was also reported in 15 patients with Alzheimer's disease who were previously refusing food. Surprisingly, THC also decreased the observed severity of disturbed behavior.[26]

In patients diagnosed with primary anorexia nervosa there was no measurable cannabinoid effect, presumably because the underlying pathological mechanism is not loss of appetite.

In the nineteenth century, cannabis was employed in indigestion and stomachache associated with appetite loss.

Nausea and Vomiting

(See Chapter 14.)

Treatment of side effects associated with antineoplastic therapy is the indication for cannabinoids which has been most documented, with about 40 studies (THC, nabilone, other THC analogues, marijuana). Most trials were conducted in the 1980s. THC has to be dosed relatively highly (5 mg/m^2 body surface, every 4 to 6 h, four times a day), so that resultant side effects may occur comparatively frequently. THC was inferior to high-dose metoclopramide in one study. There are no comparisons of THC to the modern 5-HT$_3$ (serotonin) antagonists (e.g., ondansetron, granisetron).

Whereas dronabinol has a diminished acceptance in the treatment of side effects of chemotherapy, in folk medicine cannabinoids remain popular and are often used in other causes of nausea including AIDS and hepatitis.

Glaucoma

(See Chapters 19 and 34.)

In 1971, during a systematic investigation of its effects in healthy marijuana users, it was observed that cannabis reduces intraocular pressure. In the following 12 years a number of studies in healthy individuals and glaucoma patients with marijuana and several natural and synthetic cannabinoids were conducted. Marijuana decreased intraocular pressure by an average of 25 to 30 percent, occasionally up to 50 percent, the effect lasting 4 to 6 h. Some nonpsychotropic cannabinoids (CBD, CBG, CBN), and to a lesser extent, some noncannabinoid constituents of the hemp plant also decrease intraocular pressure. A polysaccharide-containing water-soluble marijuana-derived material (MDM), and a nonpsychotropic alcoholic extract of marijuana, named Canasol, are used in the Caribbean area for glaucoma treatment.

Epilepsy

The use of cannabis in epilepsy is among its historically oldest indications. Animal experiments provide evidence of the antiepileptic effects of some cannabinoids. The anticonvulsant activity of the drugs phenytoin and diazepam have been potentiated by THC. According to a few case reports from the past three decades, some epileptic patients continue to utilize cannabis to control an otherwise unmanageable seizure disorder. Cannabis use may occasionally precipitate convulsions. In contrast to THC, there is no development of tolerance to the antiepileptic effects of CBD.

Asthma

Experiments examining the antiasthmatic effect of THC or cannabis date mainly from the 1970s, and are all acute studies. The effects of a marijuana cigarette (2 percent THC) or oral THC (15 mg), respectively, approximately correspond to those obtained with therapeutic doses of common bronchodilator drugs (salbutamol, isoprenaline). Following inhalation, the effect lasts about two hours. Since inhalation of cannabis products may irritate the mucous membranes, oral administration or another alternative delivery system would be preferable. Very few patients developed bronchoconstriction after inhalation of THC (see Figure 11.5).

Pruritus and Allergies

Pruritus is caused by a complex process, involving different neurotransmitters, the hormonal system, blood vessels of the skin, psyche, and other systems. Some aspects of this process seem to be influenced by THC and might explain positive effects reported by a number of patients. The immunomodulatory action of THC suggests an antiallergic effect (see Chapter 10).

Dependency and Withdrawal

(See Chapter 20.)

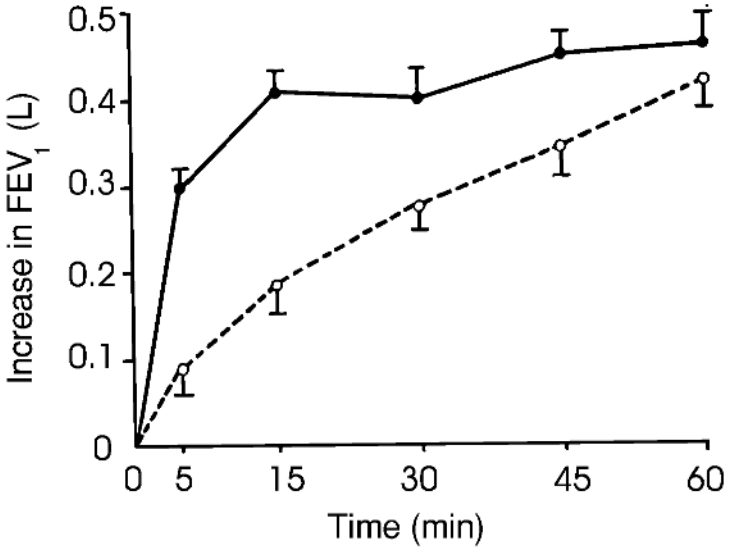
According to historical and modern case reports cannabis is a good remedy to combat withdrawal in dependency on benzodiazepines, opiates, and alcohol. For this reason, some have referred to it as a gateway drug back. In this context, both the reduction of physical withdrawal symptoms and stress connected with discontinuance of drug abuse may play a role in its observed benefits.

Psychiatric Symptoms

(See Chapter 20.)

An improvement of mood in reactive depression has been observed in several clinical studies with THC. Additional case reports claiming benefit

FIGURE 11.5. Increase in Forced Expired Volume in One sec (FEV_1) After Inhalation of 100 μg Salbutamol (Solid Line) or 200 μg THC (Interrupted Line)



Source: Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of $\triangle^1$-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax* 1976;31(6): 720-723. Reprinted with permission from the BMJ Publishing Group.

of cannabinoids in other psychiatric symptoms and diseases, such as sleep disorders, anxiety disorders, bipolar disorders, and dysthymia, also exist. Evidence suggests that positive symptoms of psychoses (delusions, hallucinations, etc.) may have origins in an increased dopaminergic activity whereas the negative symptoms (apathy, anhedonism, emotional retreat, etc.) result from enhanced cholinergic activity. The use of cannabis may eventually decrease negative symptoms and increase positive symptoms.[21] Various authors have expressed different viewpoints concerning psychiatric syndromes and cannabis. Although some emphasize the problems caused by cannabis—in the sense of a comorbid dependency problem (see Chapters 23 and 27), others promote the therapeutic possibilities in the sense of the self-medication theory [24,8] (see Chapter 20). Quite possibly cannabis products may be either beneficial or harmful, depending on the particular case. The attending physician and the patient should be open to a critical examination of the topic, and a frankness to both possibilities.

Autoimmune Diseases and Inflammation

(See Chapter 10.)

In a number of painful syndromes secondary to inflammatory processes (e.g., ulcerative colitis, arthritis), cannabis products may act not only as analgesics but also demonstrate anti-inflammatory potential. For example,

some patients employing cannabis report a decrease in their need for steroidal and nonsteroidal anti-inflammatory drugs. Moreover, some reports suggest positive effects of cannabis self-medication in allergic conditions. It is as yet unclear whether cannabis products may have a relevant effect on causative processes of autoimmune diseases.

In a study on rats, oral cannabis was effective against an infection with *Trypanosoma brucei brucei*.[19,14] Lancz and colleagues noted that incubation with THC decreased herpes simplex virus infectivity in vitro in both a time and dose dependent manner up to 80 percent, so that ointments containing THC may be of benefit in the treatment of infections with herpes simplex.[14]

Miscellaneous, Mixed Syndromes

A number of positive patient reports on medical conditions cannot be easily assigned to the previous categories, such as tinnitus, chronic fatigue syndrome, restless legs syndrome, and others (see Chapter 12). A common indication for cannabis in the nineteenth century was pain reduction during birth and support of labor, an effect occasionally used also in modern folk medicine.

Cannabis products often show very good effects in diseases with multiple symptoms. These include painful conditions that have an inflammatory origin (e.g., arthritis), or those that are accompanied by increased muscle tone (e.g., menstrual cramps, spinal cord injury), or in diseases with nausea and anorexia accompanied by pain, anxiety, and depression, respectively (e.g., AIDS, cancer, hepatitis C).

SURVEYS

In an anonymous standardized survey of 123 patients on the medical use of cannabis products in the German language area in Europe, the most frequent indications were depression, multiple sclerosis, HIV-infection, migraine, asthma, back pain, hepatitis C, sleep disorders, epilepsy, spasticity, headache, alcoholism, glaucoma, nausea, slipped intervertebral disc, and spinal cord injury[23] (see Table 11.2).

In an Australian survey with 202 participants, anxiety, stress, depression, nausea, chronic pain, muscular spasm, digestive disorders, glaucoma, nausea associated with chemotherapy, multiple sclerosis, and HIV/AIDS predominated.[11] The frequency with which indications are reported in patient surveys on the medical use of cannabis apparently does not only depend on the therapeutic efficacy of the plant but also on the availability of knowledge that patients with certain diseases receive about cannabis in a given region.

TABLE 11.2. Diagnoses of Patients in a Survey on the Medical Use of Cannabis Products (128 Patients, 167 Diagnoses = 100%, Multiple Indications Possible)

Diagnosis group	Diagnosis	n (%)
Neurological		42 (25.1)
	multiple sclerosis	18 (10.8)
	epilepsy	6 (3.6)
	spasticity	6 (3.6)
	slipped disc	4 (2.4)
	paraplegia, quadriplegia	5 (3.0)
	Tourette's syndrome	1 (0.6)
	polyneuropathy	1 (0.6)
	myopathy	1 (0.6)
Psychical		37 (22.2)
	depression	20 (12.0)
	sleep disorder	8 (4.8)
	anxiety depression	1 (0.6)
	cyclothymia	1 (0.6)
	alcoholism	5 (3.0)
	opiate dependency	2 (1.2)
Pain		35 (21.0)
	migraine	11 (6.6)
	back pain	9 (5.4)
	headache	6 (3.6)
	joint pain	3 (1.8)
	polyarthritis	2 (1.2)
	stomachache	1 (0.6)
	menstrual pain	1 (0.6)
	Bechterew's disease	1 (0.6)
	scoliosis	1 (0.6)
Infection		26 (15.6)
	HIV	15 (9.0)
	hepatitis C	8 (4.8)
	chronic bronchitis	2 (1.2)
	post polio syndrome	1 (0.6)
Miscellaneous		
	asthma	10 (6.0)
	neurodermitis	3 (1.8)
	chronic myeloic leukemia	1 (0.6)
	glaucoma	5 (3.0)
	nausea	5 (3.0)
	appetite loss	3 (1.8)

Source: Schnelle M, Grotenhermen F, Reif M, Gorter RW. Ergebnisse einer standardisierten Umfrage zur medizinischen Verwendung von Cannabisprodukten im deutschen Sprachraum [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. *Forschende Komplementârmedizin [Research in Complementary Medicine]* 1999;(Suppl 3):28-36.

In cannabis buyers' clubs in California (see Chapter 12) individuals with HIV/AIDS represented the largest group of members. In a survey among 100 members of the San Francisco Cannabis Buyers' Club by Mendelson, 60 percent of those interviewed were HIV positive.[13] The membership profile of the 739 patients of the Los Angeles Cannabis Resource Center (LACRC) showed 71 percent to be HIV infected.[13] In the Australian survey only 1.5 percent reported HIV/AIDS to be the cause for self-medication with marijuana.[11]

According to the LACRC, only 4.1 percent of members described musculoskeletal disorders or multiple sclerosis as the primary cause for their cannabis use,[13] while this spectrum represented 20 percent in the German sample. In the United Kingdom the discussion on the medical use of cannabis primarily centered around multiple sclerosis and chronic pain.[12] One reason for this discrepancy may be due to the educational activities of the Alliance for Cannabis Therapeutics founded in 1992 in the UK by MS patients. In the Australian survey 51 percent of the women stated that they used the drug for premenstrual tension and dysmenorrhea.[11]

Such regional differences may influence expert opinions on medical cannabis. While the authors of the U.S. Institute of Medicine report state that the "accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation,"[13] the report of the British House of Lords emphasizes above all the use in painful conditions and multiple sclerosis.[12]

Tables 11.3 through 11.11 present a selection of some clinical studies and case reports with cannabis and cannabinoids. The quoted literature is taken mainly from the reviews by the Association for Cannabis As Medicine[1] and the British Medical Association,[3] respectively, as well from the corresponding chapters of this book (see table sources for details).

TABLE 11.3. Nausea and Vomiting in Cancer Chemotherapy

Author	Subjects	Drug	Results
Sallan et al. (1975)	20 evaluable patients, resistant to standard drugs	THC 10 mg/m^2	Improvement in 14 patients with THC and in none with placebo
Frytak et al. (1979)	116 patients on 5-fluorouracil and semustine	THC 15 mg tid PCP 10 mg tid	THC and PCP equally effective, both better than placebo
Sallan et al. (1980)	84 patients on various cancer chemotherapy	THC 10 mg/m^2 4 hrly; PCP 10 mg 4 hrly	THC better than PCP
Orr et al. (1981)	55 patients on various cancer chemotherapy	THC 7 mg/m^2 qid; PCP 7 mg/m^2 qid	THC better than PCP

Niedhart et al. (1981)	52 patients on various cancer chemotherapy	THC haloperidol	No difference between THC and haloperidol
Gralla et al. (1984)	30 patients on cisplatin	THC 10 mg/m^2 MCP 2 mg/kg i.v.	MCP better than THC, both better than placebo
Vinciguerra et al. (1988)	74 patients on various cancer chemotherapy	Open study with marijuana	Very effective in 34%, moderately effective in 44%, not effective in 22%
Lane et al. (1991)	62 patients on various cancer chemotherapy	THC 10 mg qid PCP 10 mg qid combination	PCP better than THC; combination of PCP and THC better than single drugs
Dansak et al. (1997)	169 patients	Oral THC; smoked marijuana	Marijuana slightly superior to THC
Abrahamov et al. (1995)	8 children	Oral $\triangle^8$-THC	Prevention of emesis

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

Note: PCP = prochlorperazine; MCP = metoclopramide.

TABLE 11.4. Multiple Sclerosis (MS) and/or Spinal Cord Injury

Author	**Subjects**	**Drug**	**Results**
Dunn et al. (1974)	10 patients with spinal cord injury	Cannabis, patient reports	5 of 8 improvement of spasticity, 4 of 9 improvement of phantom limb pain
Petro (1980)	1 patient with MS 1 patient with spinal cord injury	Cannabis, open clinical report	Reduction of pain and spasticity
Petro et al. (1981)	9 patients with MS	Single doses of oral THC 5 to 10 mg	Significant reduction of spasticity
Clifford (1983)	8 patients with MS	THC 5 to 15 mg oral 6 hrly	2 patients with objective improvement of tremor, 5 patients with subjective improvement
Ungerleider et al. (1987)	13 patients with MS	Oral THC 2.5 to 15 mg once or twice daily for 5 days	Significant subjective improvement in spasticity at doses of 7.5 mg and above; no objective improvement
Meinck et al. (1989)	1 patient with MS	Smoked marijuana, single dose	Improvement of tremor, spasticity and ataxia
Malec et al. (1982)	24 patients with spinal cord injury	Cannabis, questionnaire	21 of 24 reduction of spasticity

TABLE 11.4 *(continued)*

Maurer et al. (1990)	1 patient with spinal cord injury	Oral THC 5 mg; codeine 50 mg; placebo; each given 18 times	THC and codeine alleviated pain, THC additionally spasticity
Greenberg et al. (1994)	10 patients with MS; 10 controls	Smoked marijuana (1,54%), single dose	Impairment of posture and balance; no other objective neurological changes
Martyn et al. (1995)	1 patient with MS	Oral nabilone 1 mg every second day for 2 periods of 4 weeks	Improvement of muscle spasms and frequency of nocturia
Brenneisen et al. (1996)	1 patient with MS 1 patient with cervical myelopathy	Oral THC 10 or 15 mg, Rectal THC 2.5 or 5 mg	Improvement of joint function and ability to walk; in 1 patient additional alleviation of pain
Consroe et al. (1997)	112 patients with MS	Smoked marijuana, anonymous survey	In more than 80% improvement of spasticity, pain, tremor, depression, etc.

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin*. Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

TABLE 11.5. Movement Disorders

Author	**Subjects**	**Drug**	**Results**
Consroe et al. (1986)	5 patients with dystonia	Oral cannabidiol 100-600 mg/day oral over a period of 6 weeks	20 to 50% improvement of dystonia; deterioration of tremor and hypokinesis in 2 patients with parkinsonism in doses above 300 mg/day
Sandyk et al. (1988)	3 patients with Tourette's syndrome	Smoked cannabis; case reports	Alleviation of motor tics
Frankel et al. (1990)	5 patients with Parkinson's disease	Cannabis cigarette (2%)	No improvement
Consroe et al. (1991)	15 patients with Huntington's disease	Cannabidiol 10 mg/kg/day over a period of 6 weeks	No improvement
Müller-Vahl et al. (1999)	1 patient	10 mg THC, single dose	Improvement of tics and other symptoms for a period of seven hours

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

TABLE 11.6. Pain

Author	Subjects	Drug	Results
Noyes, Brunk, Baram, et al. (1975)	10 patients with cancer	Oral THC 5 to 20 mg	Significant pain relief with 15 mg THC and more
Noyes, Brunk, Baram, et al. (1975)	36 patients with cancer	Oral THC 10 and 20 mg codeine 60 and 120 mg	Pain relief with 20 mg THC and 120 mg codeine
Raft et al. (1977)	10 patients undergoing extraction of teeth	THC 0.22 and 0.44 mg i.v.	No pain relief with THC
Petro (1980)	1 patient with MS1 patient with spinal cord injury	Cannabis, open clinical report	Relief of pain and spasticity
Jain et al. (1981)	56 patients with postoperative pain	Levonantradol 1.5 to 3 mg i.m.	Significant pain relief compared to placebo
Maurer et al. (1990)	1 patient with spinal cord injury	THC 5 mg oral; Codeine 50 mg; placebo; each 18 times	THC and codeine alleviated pain, THC also relieved spasticity
Holdcroft et al. (1997)	1 patient with familial Mediterranean fever	Cannabis extract standardized on THC, 5 times 10 mg/day for 6 weeks	Significant reduction of need in morphine with cannabis compared to placebo

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

TABLE 11.7. Anorexia and Cachexia

Author	Subjects	Drug	Results
Regelson et al. (1976)	54 patients with cancer	Oral THC 2.5 to 5 mg tid	Weight gain with THC, weight loss with placebo
Plasse et al. (1991)	10 patients with AIDS	THC 2 × 2.5 mg for 5 months	Significant weight gain
Conant et al. (1991)	19 patients with AIDS	THC 2 × 2.5 to 3 × 5 mg for 4 weeks	No clear result
Plasse et al. (1992)	40 patients with cancer	THC 1 × 2.5 to 2 × 5 mg	Significant reduction of weight loss
Gorter et al. (1992)	12 patients with AIDS	THC 2×2.5 to 4x5 mg for 4 to 20 weeks	Weight gain

TABLE 11.7 *(continued)*

Nelson et al. (1994)	19 patients with cancer	THC 3×2.5 mg for 4 weeks	Positive influence on weight
Beal et al. (1995)	139 patients with AIDS	THC 2×.5 mg for 6 weeks	Weight gain
Timpone et al. (1997)	52 patients with AIDS	THC 2×2.5 mg; megestrol acetate 750 mg;THC 2×2.5 mg plus 750 mg megestrol acetate;THC 2×2.5 mg plus 250 mg megestrol acetate	Weight loss with THC, weight gain with megestrol acetate
Beal et al. (1997)	94 patients with AIDS	THC 1 to 2×2.5 mg for 12 months	Tendency to stable weight for 7 months
Volicer et al. (1997)	15 patients with Alzheimer's disease	Oral THC and placebo cross-over for 6 weeks	Higher weight gain in verum periods

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

TABLE 11.8. Epilepsy

Author	**Subjects**	**Drug**	**Results**
Consroe et al. (1975)	1 patient with generalized epilepsy	Smoked cannabis 2 to 5 times daily and continuation of standard medication	No improvement with cannabis
Cunha et al. (1980)	15 patients with generalized epilepsy	Oral cannabidiol 200 to 300 mg/day plus standard medication	Improvement in 7 of 8 with cannabidiol; 1 of 7 with placebo
Ames et al. (1986)	12 patients	Oral cannabidiol 300 mg/day for 6 months plus standard medication	No effect of cannabidiol
Trembly et al. (1990)	10 patients	Oral cannabidiol 300 mg/day for 6 months plus standard medication	No effect of cannabidiol
Trembly et al. (1990)	1 patient	Oral cannabidiol 900 to 1200 mg/day for 10 months	Reduction of seizure frequency with cannabidiol

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

TABLE 11.9. Intraocular Pressure

Author	Subjects	Drug	Results
Hepler et al. (1971)	11 healthy subjects	2 grams of smoked marijuana (0.9%)	16 to 45% reduction of IOP in 9 of 11
Flom et al. (1975)	15 healthy subjects	Smoked THC 12 mg	IOP reduction in 7 of 15
Hepler et al. (1976)	429 healthy subjects	Smoked THC; Oral THC 15 to 40 mg	Dose dependent reduction of IOP
Hepler et al. (1976)	11 patients with glaucoma	Smoked THC (1 to 4%) oral THC 15 mg	Dose dependent reduction of IOP in 7, no effect in 4
Perez-Reyes et al. (1976)	12 healthy subjects	Infusions with different cannabinoids	Reduction of IOP with Δ^9-THC,Δ^8-THC, 11-OH-Δ^9-THC; low effect with CBN and CBD
Cooler et al. (1977)	10 healthy subjects	Infusion of 1.5 or 3 mg THC	Reduction of IOP; anxiety, increase of heart rate
Jones et al. (1981)	13 healthy subjects	Oral THC 10 to 30 mg 4 hrly	Reduction of IOP; tolerance within 10 days; rebound following abrupt withdrawal
Crawford et al. (1979)	16 patients with glaucoma	Smoked cannabis 25 mg	Drop of IOP drop parallel with drop in blood pressure
Merritt et al. (1980)	18 patients with glaucoma	Smoked THC (2%)	Drop of IOP; hypotension
Merritt, Olsen et al. (1981)	8 patients with glaucoma	THC eye drops into one eye	Dose dependent reduction of IOP in both eyes

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

Note: IOP = intraocular pressure.

TABLE 11.10. Asthma

Author	Subjects	Drug	Results
Tashkin et al. (1974)	10 asthmatic subjects	Smoked marijuana (2%) oral THC 15 mg	Marijuana and oral THC improved ventilation
Tashkin et al. (1975)	8 asthmatic subjects with induced bronchospasm	Smoked marijuana 10 mg	Relief of spasm within 10 min
Vachon et al. (1976)	17 asthmatic subjects	Smoked THC (0.9 and 1.9%)	Significant bronchodilation

TABLE 11.10 *(continued)*

Williams et al. (1976)	10 asthmatic subjects	THC aerosol (0,2 mg)	THC produced bronchodilation as effective as salbutamol
Tashkin et al. (1977)	5 asthmatic subjects 11 healthy subjects	THC aerosol 5 to 20 mg smoked THC 20mg oral THC 20 mg	THC effective in healthy subjects and 3 asthmatic subjects; aerosol caused bronchoconstriction and cough in 2 asthmatic subjects

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

TABLE 11.11. Psychiatric Symptoms and Mood

Author	**Subjects**	**Drug**	**Results**
Mikuriya (1970)	1 alcohol dependent patient	Self-medication with cannabis, psychotherapy	Quit of alcohol abuse, social reintegration
Beal et al. (1995)	139 patients with AIDS	THC 2×2.5 mg for 6 weeks	Improvement of mood (visual analogue scale)
Zuardi et al. (1995)	1 patient with psychosis	CBD with increasing doses up to 1,500 mg for a period of 4 weeks	Good antipsychotic effect
Volicer et al. (1997)	15 patients with Alzheimer's disease	Oral THC and placebo cross-over for 6 weeks	Decrease of disturbed behavior with THC
Grinspoon, Bakalar (1998)	Case reports in bipolar disorders	Self-medication with cannabis	Improvement of mania, depression or both

Source: Association for Cannabis As Medicine, ed. *Cannabis und Cannabinoide als Medizin.* Congress report (in German). Cologne: Nova-Institute, 1998; British Medical Association. *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

REFERENCES

1. Association for Cannabis as Medicine, ed. *Cannabis und Cannabinoide als Medizin*. Congress report (in German). Cologne: Nova-Institute, 1998.

2. Barsch G. Zur therapeutischen Anwendung von Cannabis: Ergebnisse einer Pilotstudie unter HIV-positiven und Aids-kranken Männern und Frauen. In Deutsche Aids Hilfe, ed. *Cannabis als Medizin. Beiträge auf einer Fachtagung zu einem drängenden Thema,* pp. 15-22. Berlin: Aids-Forum D.A.H, 1996.

3. British Medical Association *Therapeutic uses of cannabis.* Amsterdam: Harwood Academic Publishers, 1997.

4. Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology* 1983;13(6):669-671.

5. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 1997;38(1): 44-48.

6. Consroe P, Tillery W, Rein J, Musty RE. Reported Marijuana effects in patients with spinal cord injury. In *1998 Symposium on the Cannabinoids.* Burlington, VT: International Cannabinoid Research Society, 1998, p. 64.

7. Dansak DA. As an antiemetic and appetite stimulant in cancer patients. In Mathre ML, ed. *Cannabis in medical practice: A legal, historical and pharmacological overview of the therapeutic use of marijuana.* Jefferson, NC: McFarland & Co, 1997, pp. 69-83.

8. Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: Anecdotal evidence and the need for clinical research. *Journal of Psychoactive Drugs* 1998;30(2):171-177.

9. Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine.* New Haven, CT: Yale University Press, 1993.

10. Grotenhermen F, Huppertz R. *Hanf als Medizin: Die Wiederentdeckung einer Heilpflanze.* Heidelberg: Haug-Verlag, 1997.

11. Helliwell D. GPs are key informants in medicinal cannabis survey. *GP Speak, Newsletter of the Northern Rivers Division of General Practice,* April 1999, p.4.

12. House of Lords Select Committee on Science and Technology. *Cannabis: The scientific and medical evidence.* London: The Stationery Office, 1998.

13. Joy JE, Watson SJ, Benson JA, eds. *Marijuana and medicine: Assessing the science base.* Washington, DC: Institute of Medicine, National Academy Press, 1999.

14. Lancz G, Specter S, Brown HK. Suppressive effect of delta-9-tetrahydrocannabinol on herpes simplex virus infectivity in vitro. *Proceedings of the Society for Experimental Biology and Medicine* 1991;196(4):401-404.

15. Mathre ML, ed. *Cannabis in medical practice: A legal, historical and pharmacological overview of the therapeutic use of marijuana.* Jefferson, NC: McFarland & Co, 1997.

16. Mechoulam R, ed. *Cannabinoids as therapeutic agents.* Boca Raton, FL: CRC Press, 1986.

17. Mikuriya TH. Cannabis substitution. An adjunctive therapeutic tool in the treatment of alcoholism. *Medical Times* 1970;98(4):187-191.

18. Müller-Vahl KR, Kolbe H, Dengler R. Gilles de la Tourette-Syndrom. Einfluß von Nikotin, Alkohol und Marihuana auf die klinische Symptomatik. *Nervenarzt* 1997;68:985-989.

19. Nok AJ, Ibrahim S, Arowosafe S, Longdet I, Ambrose A, Onyenekwe PC, Whong CZ. The trypanocidal effect of Cannabis sativa constituents in experimental animal trypanosomiasis. *Veterinary and Human Toxicology* 1994;36(6):522-524.

20. Noyes R, Baram DA. Cannabis analgesia. *Comprehensive Psychiatry* 1974; 15(6):531-535.

21. Peralta V, Cuesta MJ. Influence of cannabis abuse on schizophrenic psychopathology. *Acta Psychiatrica Scandinavica* 1992;85(2):127-130.

22. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacology, Biochemistry and Behavior* 1991;40(3):695-700.

23. Schnelle M, Grotenhermen F, Reif M, Gorter RW. Ergebnisse einer standardisierten Umfrage zur medizinischen Verwendung von Cannabisprodukten im deutschen Sprachraum, [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. *Forschende Komplementärmedizin [Research in Complementary Medicine]* 1999;(Suppl 3): 28-36.

24. Schneier FR, Siris SG. A review of psychoactive substance use and abuse in schizophrenia: Patterns of drug choice. *Journal of Nervous and Mental Disease* 1987;175(11):641-652.

25. TNO Preventie en Gezondheid. *Aard en omvang van Cannabis gebruik bij mensen met Multiple Sclerose*. JA Deft, The Netherlands: TNO 1998.

26. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 1997;12(9):913-919.

27. Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of Δ^1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax* 1976;31(6):720-723.

Chapter 12

Medical Use of Cannabis: Experience in California

Dale Gieringer

Cannabis is currently used for medical purposes by an estimated 15,000 patients under California's medical marijuana law, Proposition 215. Its use was popularized by "cannabis buyers' clubs," which were originally heavily oriented toward AIDS patients. However, recent surveys show a growing majority of patients with other conditions, notably chronic pain and mood disorders. Over 250 separate indications for medical cannabis have been reported in interviews of 2,480 patients by Mikuriya (see Table 12.2). For many patients, cannabis clubs may afford distinctive therapeutic benefits not available through a conventional pharmacy.

EFFECTS OF PROPOSITION 215

The San Francisco Cannabis Buyers' Club (SF CBC) served as the initial headquarters for the California initiative to legalize medical marijuana. Proposition 215 was passed in the light of widespread popular understanding that marijuana had medical value, especially for cancer, AIDS, and glaucoma. Campaign polls indicated that 31 percent of the electorate personally knew of someone who used cannabis for medical purposes (Bill Zimmerman, personal communication).

Proposition 215 did not actually "legalize" medical marijuana in the sense of establishing a legal prescription distribution system, since this would have been impossible under federal law—Proposition 215 was bitterly opposed by U.S. drug enforcement authorities. Rather, it decriminalized it by giving individual patients and their caregivers the right to use, possess, and cultivate cannabis for personal medical use given a physician's recommendation. Contrary to popular misconception, Proposition 215 did

not legalize cannabis patients' clubs, whose legal status remained problematic. Although many work successfully with support of local government (at the time of composing this chapter in 1999), others have been shut down by hostile authorities.

Experience has largely refuted the two major objections of Proposition 215 opponents: that it was so loosely written as to effectively legalize cannabis in California, and that it would encourage widespread youth drug abuse. In fact, since the passage of Proposition 215, the number of marijuana arrests has risen by 6 percent, and the number of marijuana prisoners has increased 10 percent in California. Meanwhile, the 1998 Household Survey of Drug Abuse showed that marijuana use by twelve- to seventeen-year-olds in California has held steady at around 6.8 to 7.4 percent over the past several years, and is somewhat less than the national average of 8.3 percent.[7] In 1999 there were 15 clubs with 200 or more members in California, largely in the more sympathetic, but less populous, northern half of the state. Their total combined enrollment was around 9,000 members, somewhat less than the 12,000 reported in 1996 in the heyday of the SF CBC. An unknown number of patients do not belong to any club. A reasonable estimate of the present patient population might therefore be on the order of 15,000, or about 1 percent of California's total marijuana using population.

USAGE SURVEYS

Surveys of cannabis buyers' club (CBC) members show that cannabis is used for a wide variety of indications. Initial reports from the SF CBC showed a high concentration of people with AIDS. A 1993-1995 survey of 351 randomly-selected members of the SF CBC found that 87 percent (N = 305) had a medically verified illness, of whom fully 84.5 percent (N = 258) were HIV positive, a majority being diagnosed with AIDS.[1] Approximately 2 percent each were diagnosed with multiple sclerosis (N = 6) or severe musculoskeletal disorders (N = 7); another 11 percent (N = 34) were diagnosed with conditions such as cancer, glaucoma, or other diseases. The sample closely reflected the gender and age distribution of San Francisco's AIDS population (90 percent male and a median age of 36).

More recent surveys from other clubs reveal a far more diverse population. Table 12.1 summarizes two surveys by Mandel of members of the Oakland Cannabis Buyers' Cooperative (OCBC) (Mandel, 1997 and 1998, unpublished). Mandel's first survey, in 1997, found a preponderance of AIDS patients. This is not surprising, since the OCBC absorbed a heavy influx of patients from San Francisco when the SF CBC was first (temporarily) closed in 1996-1997. More recently, Mandel's data show that the population of people with AIDS has declined to 29 percent and is now smaller than those with chronic pain and related disorders (40 percent, by Mikuriya's

classification in Table 12.2). This difference may be due to several factors: (1) a heightened appreciation among physicians of cannabis' utility for other conditions; (2) an exodus of former SF CBC members to new clubs in San Francisco, and (3) a decline in the number of PWAs with wasting syndrome due to the advent of protease inhibitors.

Proposition 215 deliberately authorized an open-ended spectrum of indications for cannabis, to wit: "treatment of cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or any other illness for which marijuana provides relief." This is identical to the treatment under U.S. law of other drugs, which may be legally prescribed for any indication the physician deems appropriate once they have been approved by the U.S. Food and Drug Administration (FDA). In practice, medical acceptance of cannabis has been strongest for nausea due to cancer chemotherapy and AIDS wasting syndrome, the two indications for which THC (Marinol) is approved by the FDA. Greater reluctance to recommend cannabis for chronic

TABLE 12.1. Oakland Cannabis Buyers' Cooperative Patient Survey by J. Mandel

Primary Indication	**N 1997[3] (%)**	**N 1998[4] (%)**
AIDS/HIV	54	29
Mood disorders	9	15
Arthritis, rheumatism	7	14
CNS, inflammatory[1]	7	7
Injury, amputation, discs/back	6	15
Glaucoma, eye disease	5	2
Cancer	5	6
Digestive	2	4
Other	5	8[2]

1 CNS = central nervous system; includes migraines, multiple sclerosis.
2 Includes circulatory system 1%; respiratory 2%; genito-urinary 1%; hepatitis 1%; skin 0.4%.
3 N1997 = 768 "Core members" (four or more purchases in 1997).
4 N1998 = 965 "Current members" (registered between April 1998 and April 1999); N1998 includes: 743 male, 222 female; age distribution: <45 (N = 507), 45 to 54 (N = 325), 55 to 64 (N = 88), ≥65 (N = 44)

TABLE 12.2. Summary of 2,480 Medical Marijuana Patients, Interviewed by T. Mikuriya and Tabulated by D. Gieringer (1999)

ICD-9 Diagnostic Category	n	%
Nausea and Appetite Loss		
Total	113	4.6
Hepatitis	42	
AIDS/HIV	25	
Cancer (includes chemotherapy patients w/ nausea and others w/ postoperative pain, etc.)	29	
Nausea, other	17	
Spasms, Convulsions		
Total	228	9.2
Head, brain injury	45	
Epilepsy	25	
Spasm	23	
Quadraplegia/paraplegia	21	
Lower back pain	20	
Multiple sclerosis	15	
Colitis	19	
Pylorospasm	9	
Post-Polio	7	
Others (cerebral palsy, Tourette's, etc.)	44	
Analgesia / "Immunomodulatory Anti-Inflammant"		
Total	1133	45.7
Migraine and Neuralgias		
Subtotal	179	7.2
Migraine	127	
Neuropathy	22	
Sinusitis	12	
Psychogenic pain	5	
Other pain, neuralgias	13	
Arthritis		
Subtotal	433	17.5
Arthritis, posttraumatic	318	
Arthritis, degenerative	37	

Fibromyalgia	21	
Arthropathy	22	
Myofascial pain	11	
Rheumatoid arthritis	10	
Psoriatic arthritis	5	
Other arthritis (includes lupus, polyarthritis, etc.)	9	
Spinal and Skeletal Disorders		
Subtotal	366	14.8
Lumbosacral back disease	175	
Disks and vertebra diseases	88	
Scoliosis	33	
Spondylolisthesis	12	
Spinal stenosis	7	
Spondylosis	6	
Other spinal	12	
Sacrum disorder	11	
Other skeletal	22	
Injury, Trauma		
Subtotal	57	2.3
Sprain, whiplash	36	
Carpal tunnel	12	
Other trauma	9	
Gastrointestinal		
Subtotal	68	2.7
Gastritis	50	
Peptic ulcer	10	
Crohn's Disease	5	
Other intestinal	3	
Other Inflammatory		
Endometriosis, panniculitis, pruritis, etc.	30	1.2
Mood Disorders		
Total	660	26.6
Post-traumatic stress disorder	274	
Depression	162	
Anxiety disorder	73	

Dysthymic disorder	46		
Bipolar disorder	34		
Schizophrenia	26		
Attention deficit disorder	15		
Obsessive-compulsive disorder	8		
Panic disorder	5		
Other psychiatric	17		
Insomnia			
Total	71		2.9
Harm Reduction / Substitution			
Total	136		5.5
Alcohol dependency	118		
Opiate dependency	8		
Others	10		
Glaucoma and Eye Diseases			
Total		24	1.0
Glaucoma		15	
Others (drusen cyst, disease of conjunctiva, etc.)		9	
Asthma			
Total		53	2.1
Miscellaneous			
Total		62	2.5
Premenstrual stress		24	
Lyme disease		8	
Hypertension		7	
Others (tinnitus, Ménière's disease, diabetes, chronic fatigue syndrome, etc.)		23	

pain and mood disorders exists. Although they were among the most common therapeutic applications in the nineteenth century, they have been largely neglected in modern clinical research.[3] Recently, interest in this area has been reawakened by the findings of analgesic activity in cannabinoids (see Chapter 8), and confirmed by the report of the U.S. Institute of Medicine, which found chronic pain to be a condition for which smoked cannabis could have unique therapeutic benefits.[6]

Chronic pain and mood disorders figure prominently among the wide variety of applications for which marijuana is being used. This is evidenced in data from 2,480 patients interviewed by Tod Mikuriya, a psychiatrist who specializes in Proposition 215 cases (see Table 12.2). Altogether, Mikuriya has recorded more than 250 separate indications for cannabis under the *International Classification of Diseases* Ninth Revision (ICD-9) system. All (100 percent) of the patients interviewed by Mikuriya had been diagnosed with chronic conditions. Nearly all (99 percent) had tried conventional pharmacotherapy and experienced adverse effects. The great majority were diagnosed with multiple ICD-9 indications. The overwhelming majority also reported prior, nonmedical experience with cannabis, evidence that medicinal use of cannabis is in some respects a cultural phenomenon.

Table 12.2 summarizes Mikuriya's data in categories based on primary ICD-9 diagnosis. Because Mikuriya's research specializes in patients outside the normal indications, AIDS and cancer patients are underrepresented in his survey. Only indications with five or more mentions are itemized separately in Table 12.2; the rest, comprising over 150 ICD-9 diagnoses, are lumped under the category "other." The latter include a remarkable variety of rare and idiosyncratic conditions, e.g., eosinophilia myalgia syndrome, Henoch-Schönlein purpura, osteochondrosis, Kashin-Bek disease, Ménière's disease, Tietze's disease, patellar chondromalacia, bruxism, and others.

In scattered cases, patients report surprising benefits for such everyday indications as stuttering, diabetes, hypertension, color blindness, etc. Such reports may be idiosyncratic, spurious or psychosomatic in origin. Because cannabis has a broad psychoactive, euphoriant effect, many patients may feel better without any other detectable relief of symptoms. In such cases, cannabis may be a magnifier of the placebo effect.

By far, the largest category of patients interviewed by Mikuriya use cannabis for analgesia to treat conditions including: migraines and neuralgias; arthritis and rheumatism; spinal, skeletal and back disorders due to injury, deformity, or degenerative disease; inflammatory gastrointestinal disorders, and a host of miscellaneous diseases. Mikuriya observes that many of the underlying conditions are characterized by inflammatory autoimmune dysfunction, whether idiopathic, congenital, or acquired due to injury. Mikuriya accordingly refers to cannabis as an "immunomodulatory anti-inflammatory analgesic."

The second largest category in Table 12.2 are patients with mood disorders, particularly posttraumatic stress disorder, depression, dysthymia, bipolar syndrome, and schizophrenia. The medical community has been reluctant to accept the use of cannabis in these disorders. This is partly due to a lack of clinical research on cannabis's efficacy, and concerns that cannabis may actually aggravate certain mental disorders such as depression and schizophrenia. In California the reluctance is partly due to doubts over the

extent to which mental disorders are legally protected under Proposition 215. Nonetheless, a substantial number of Proposition 215 patients and physicians are using cannabis to treat mood disorders.

Another use of cannabis noted by Mikuriya is as a harm reduction substitute for other, more harmful drugs. This occurs in two ways. First, patients with substance abuse problems use marijuana to replace other drugs of abuse to reduce adverse health or behavioral problems due to adverse effects of the drugs and withdrawal. The largest number of such patients are alcoholics, who constituted 5 percent of Mikuriya's interviewees. Second, many patients find that marijuana effectively replaces other prescription drugs and analgesics (notably opiates) which would otherwise be prescribed to treat their disease and which have worse side effects. This kind of use, though universal among patients with chronic pain, is not reflected in Table 12.2, since it does not qualify as a "primary indication."

Marijuana is widely used as a harm reduction aid by CBC patients. This can be seen in the results of an uncontrolled survey of 100 SF CBC members by a University of California at San Francisco research team[5] (see Table 12.3).

The survey was heavily biased towards indigent patients, since subjects were recruited by offering money for participation. Fully 87 percent had a history of substance abuse problems. A majority had multiple disorders; 60 percent were PWAs, and 27 percent reported psychiatric problems. This sampling represents an important subpopulation of very sick patients with chronic physical, mental, and social problems. In addition to chronic disease and substance abuse, many suffer from social isolation, poverty, unemployment and/or homelessness.

For this population, the availability of cannabis in the social setting of a club can afford distinctive therapeutic benefits not available through a conventional pharmacy. In addition to medicine, clubs provide social support, services, activities, and a feeling of connectedness to others.[2] This suggests that the full therapeutic potential of cannabis cannot be realized within the narrow bounds of a pharmaceutically dispensed Schedule II prescription drug, and that cannabis should also be available in a demedicalized, over-the-counter social setting, as argued by Grinspoon.[4]

The high proportion of AIDS patients reflected the fact that the AIDS community was highly organized and politicized, and that most PWAs were already familiar with marijuana as a recreational drug, either as members of the gay community or as intravenous drug users. Surveys of PWAs in California, Hawaii, Alabama, and Australia found that some 25 percent to 37 percent of respondents used marijuana medically.[8]

TABLE 12.3. San Francisco Cannabis Buyers' Club: 100 Members

Indication	n
AIDS	60
Musculoskeletal, Arthritis	39
Psychiatric Disorders	27
Neurological Disorders	9
Gastrointestinal	7
Others*	7
Multiple	59
History of Drug Dependence	87

Source: Harris D, Jones R, Mendelson J. *A survey of 100 medical marijuana club members.* Presented at the College on Problems of Drug Dependence, Scottsdale, Arizona, June 1998.

*Includes cancer, glaucoma, Reiter's Syndrome, nephrolithiasis, etc.

REFERENCES

1. Brown J, Beck J, Mandel J, Feldman H, Apostolides M, Mikuriya T, Hernandez V. Unpublished letter, 1996.

2. Feldman H, Mandel J. Providing medical marijuana: The importance of cannabis clubs. *Journal of Psychoactive Drugs* 1998;30(2):179-886.

3. Gieringer D. Review of human studies on medical use of marijuana. In Rosenthal E, Gieringer D, Mikuriya T. *Marijuana Medical Handbook.* Oakland, CA: Quick Publishing, 1997.

4. Grinspoon L. Medical marijuana in a time of prohibition. *International Journal of Drug Policy* 1999;10:145-156.

5. Harris D, Jones R, Mendelson J. *A survey of 100 medical marijuana club members*. Presented at the College on Problems of Drug Dependence, Scottsdale Arizona, June 1998.

6. Joy JE, Watson SJ, Benson JA, eds. *Marijuana and medicine: Assessing the science base*. Institute of Medicine. Washington, DC: National Academy Press, 1999.

7. Substance Abuse and Mental Health Statistics, Office of Applied Studies: <http://www.samhsa.gov/oas>.

8. Wesner B. "The medical marijuana issue among PWAs." Drug Policy Foundation. Student paper, Stephen Sidney, 1997.

Chapter 13

Anorexia and Cachexia

Martin Schnelle
Florian Strasser

The term "cachexia" refers to the dramatic weight loss that is characteristic of several systemic diseases, including malabsorption, congestive heart failure, major trauma, severe sepsis, AIDS, and cancer. Cachexia is characterized by unintentional weight loss involving depletion of skeletal muscle mass and adipose tissue and contributes significantly to mortality. Anorexia (meaning loss of appetite)—as a frequent complication of these diseases—is a major contributor to the development of cachexia.

Although incompletely understood, common mechanisms are likely to underlie the development of anorexia/cachexia associated with these diseases. In contrast to simple starvation, the weight loss in anorexia/cachexia is not only a result of reduced food intake. Complex interactions among the nervous, endocrine, immune, and other systems determine derangement in host metabolism involving metabolic rates as well as the processing of virtually all metabolic substrates. Abnormalities in all of these systems have been implicated in the multifactorial pathophysiology of weight loss associated with anorexia/cachexia.

This chapter refers only to the anorexia/cachexia syndrome in cancer and to the wasting syndrome in AIDS.

ANOREXIA AND CACHEXIA IN CANCER PATIENTS

The extremely complex anorexia-cachexia syndrome is, together with cancer pain, one of the two most frequent and devastating problems that affect patients with advanced and terminal cancer. Cancer-cachexia, which is associated with symptoms such as anorexia, chronic nausea, asthenia, and changes in body image, does not have to be accepted as a normal event in

terminal cancer, as pain has been rejected as a normal event in advanced stages of this disease.[9]

Many cancer patients exhibit unexplained weight loss as the first symptom of their disease. Patients with pancreatic and gastric cancer have the highest frequency of weight loss (nearly 90 percent), in contrast to patients with breast cancer and hematological malignancies such as non-Hodgkin's lymphoma (about 30 percent).[14]

MECHANISMS OF CANCER CACHEXIA

The interpretation of cachexia as the result of increased caloric demand to "nourish" the tumor is obsolete. A tumor/host competition for nutrients is unlikely, since cachexia can be absent in patients with very large tumors or can occur when the tumor mass represents less than 0.01 percent of the host weight.

Cachexia is not a local effect of a tumor, but is thought to arise from distant metabolic effects, i.e., it is a type of paraneoplastic syndrome. The results of a number of clinical and laboratory studies suggest that the action of cytokines (tumor necrosis factor-alpha, interleukin-6, interleukin-1, interferon-gamma, and leukemia inhibitory factor)[33] alone is unable to explain the complex mechanism of wasting in cancer cachexia. Tumor-derived catabolic factors such as lipid mobilizing factor[22] and protein mobilizing factor,[25] which act directly on skeletal muscle and adipose tissue, may also be involved.

Many other factors can be related to the multifactorial etiology of anorexia-cachexia, such as pain, learned food aversion, anxiety and depression,[7] sensory changes including olfactory and taste abnormalities, decreased gastric emptying, nausea and vomiting, diarrhea and constipation, mucositis, and direct anatomic effect of tumors (impaired swallowing, obstruction, malabsorption).[4]

In contrast to simple starvation, in which more than 75 percent of weight loss is from body fat, in cancer cachexia, weight loss is due to approximately equal losses of fat and body cell mass, particularly of skeletal muscle.[5] Increasing nutrient intake including aggressive nutritional therapy is unable to reverse the anorexia-cachexia syndrome.[23] Despite declining food and energy intake, patients with anorexia-cachexia have accelerated catabolism, with either normal or increased resting energy expenditure.[21]

ANOREXIA AND CACHEXIA IN AIDS PATIENTS: WASTING SYNDROME

Anorexia and cachexia associated with HIV infection, usually called the wasting syndrome, commonly arise in HIV-infected patients. The HIV

wasting syndrome was categorized as an AIDS-defining illness in 1987. Wasting may be less severe in patients receiving highly active antiretroviral therapy (HAART). Before such therapy was available, two thirds of men with AIDS weighed less than 90 percent of their ideal body weight or lost more than 10 percent of their usual weight.[13] However, weight gain associated with the use of proteinase inhibitors, part of HAART, is often due to redistribution of fat in a dorsocervical pattern ("buffalo neck") and a truncal pattern, with no change in lean body mass.[11]

Mechanisms of AIDS Wasting

The AIDS wasting syndrome is also multifactorial in etiology as is the case with cancer anorexia-cachexia. The etiologies can be divided into the broad categories of hypermetabolism (increased utilization of carbohydrates and proteins, resulting in accelerated loss of lean body mass); decreased oral intake (anorexia, pharyngeal/esophageal disease, depression/dementia); malabsorption (diarrhea from gastrointestinal pathogens, HIV enteropathy and from anti-HIV medication); cytokine effects (elevated levels of TNFα, interleukin 1 and 6); and endocrine abnormalities (lowered levels of testosterone, thyroid and adrenal insufficiency and growth hormone deficiency are in discussion).[12]

Catabolism of body cell mass leading to wasting in HIV infection does occur despite undetectable viral loads; therefore, body cell mass must be monitored and treated independently of viral load.[1] Clearly, wasting is an independent risk factor to both morbidity and mortality in AIDS.[30]

Clinical Findings

Cachectic patients present with a number of devastating symptoms including anorexia, chronic nausea, early satiety, constipation, asthenia, decreased motor and mental skills, decline in attention span and concentration abilities, and change in body image.[4] All these symptoms seem to have impact on the general quality of life of the patients.[8]

The presence of anorexia is an extremely distressing syndrome because appetite and the ability to eat have been reported to be one of the most important factors in the physical and psychological aspects of a patient's quality of life.[29]

In cancer patients receiving chemo- or radiotherapy, and in AIDS patients, mucositis, mouth ulcers and candidiasis (oral and esophageal) are often present which further impair food intake and taste. The symptoms of delayed gastric emptying (early satiety, postprandial fullness, eructation) can be exacerbated by narcotic analgesic use and serotonin antagonists used as antiemetics.

Pharmacological Approaches to Anorexia/Cachexia

In general, therapeutic interventions for cancer cachexia and AIDS wasting have either focused on optimizing nutritional intake (enteral/parenteral nutrition, appetite stimulation, prokinetics) or have attempted to address the underlying metabolic alterations (inflammation, cytokines, hormones) beside the treatment of the underlying disease with chemo- or radiotherapy and HAART, respectively. For effective treatment adequate symptom assessment should be performed to quantify the symptom and characterize the main constraints to be relieved.

Enteral/parenteral nutrition. Numerous studies in patients with advanced cancer have demonstrated that aggressive nutritional therapy does neither significantly influence the outcome (improvement of survival, tumor response, chemotherapy-toxicity) nor improve symptom control and performance status, i.e., quality of life.[6,21] Nutrition-based strategies have been developed as well for the treatment of patients with AIDS wasting but conflicting results have been obtained in studies in which both an increase in body weight and continuing weight loss have been shown (summarized by Corcoran and Grinspoon[13]).

Corticosteroids. In the past, corticosteroids have been the first-line agents used for appetite stimulation in cancer cachexia. Dexamethasone, methylprednisolone and prednisolone are agents that have been evaluated in randomized, double-blind, placebo-controlled trials (summarized by Gagnon and Bruera[17]). All researchers have shown a limited effect of corticosteroids of up to four weeks on appetite, food intake and performance status. Chronic use of these compounds is associated with a number of limiting side effects including exacerbation of progressive muscle wasting and weakness, immunosuppression, diabetes, osteoporosis, and mental status changes.[17] Because of their immunosuppressive properties, corticosteroids are contraindicated in the treatment of AIDS wasting.

Progestational agents. The mechanisms of action of megestrol acetate (MA) and medroxyprogesterone acetate (MPA) in appetite stimulation and weight gain observed in cachectic patients may be related to central appetite stimulation, anabolic effects and probably cytokine modulation.[26] MA has demonstrated a dose-related increase on appetite, food intake, and body weight in both cancer and AIDS patients. Adverse effects which limit the use of MA and MPA include thromboembolic disease, glucose intolerance, fluid overload and hypertension (summarized by Ottery et al.[28]).

Metabolic inhibitors. Three randomized, placebo-controlled trials failed to demonstrate any body weight gain in patients with advanced cancer treated with hydrazine sulfate. This compound, which blocks catabolic pathways, caused significant deterioration in quality of life because of its toxicity (summarized by Gagnon and Bruera[17]). No clinical trials with hydrazine sulfate in AIDS patients have been reported to date.

Gastrointestinal motility stimulants. Gastrokinetic agents may be helpful in anorexia accompanied by early satiety. In addition to some promising results with metoclopramide (summarized by Gagnon and Bruera[17]), the role of the other prokinetic agents (cisapride, domperidone, and newer agents such as 5-HT-4-agonists) remains to be clarified. No clinical trials with prokinetic agents in AIDS patients have been reported so far.

Anabolic-androgenic steroids. Two prospective randomized trials in cachectic cancer patients failed to show an improvement of weight with anabolic androgens (fluoxymesterone[24] and nandrolone decanoate[28]). In a double-blind study that evaluated effects of the testosterone analogue oxandrolone in 50 AIDS patients with wasting, a nonsignificant increase in body weight was reported.[28]

Human growth hormone. Recombinant human growth hormone (rhGH) alters metabolism by increasing mobilization and oxidation of fat, reducing oxidation of protein, and thereby increasing lean body mass. Clinical trials with rhGH in cancer populations have not been reported so far. In a long-term study of rhGH in 178 weight-losing HIV-infected patients an immediate anabolic effect with a significant, but only transient, gain in lean body mass has been demonstrated.[28]

Thalidomide. Animal and human studies have suggested that thalidomide is a selective inhibitor of TNF-α production. In cancer patients with anorexia-cachexia preliminary data show improvement of general well-being and of several symptoms such as difficulty falling asleep, insomnia, nausea, anorexia, and asthenia with few side effects.[10] A placebo-controlled trial in 28 patients with AIDS wasting showed a significant body weight gain and reversed the wasting process.[28] Limiting adverse effects associated with thalidomide are sensory neuropathy, constipation, sedation, hypersensitivity reactions and, of course, its teratogenic effects.

Melatonin. This is a pineal hormone that regulates circadian rhythm and decreases the level of circulating TNF-α. One controlled, but not double-blind, clinical trial in 100 patients with metastatic solid tumors showed improvement of anorexia and cachexia.[28] There are no data for the use of melatonin in AIDS wasting.

Omega-3 fatty acids (Eicosapentanoic acid). The polyunsaturated fatty acid eicosapentanoic acid (EPA) has been shown to inhibit lipolysis and protein degradation associated with cachexia.[28] In an open study[37] with a supplement of fish oil capsules, EPA and docosahexanoic acid (DHA), pancreatic cancer patients showed a small body weight gain compared with a previous weight loss (see also Chapter 38). In men with HIV-wasting syndrome no significant improvement in food intake, body weight, or lean body mass was found using dietary n-3 fatty acid supplementation.[19]

Other agents for the treatment of cancer anorexia-cachexia and AIDS wasting are cyproheptadine, an antihistamine agent with serotonin antago-

nist and appetite-stimulating properties; β_2-adrenoceptor agonists, which demonstrate a positive effect on muscle mass in tumor-bearing rats; and nonsteroidal anti-inflammatory drugs which may produce body weight gain in cancer patients.[17]

CANNABIS, Δ^9-THC, AND CANCER CACHEXIA/AIDS WASTING

History, Anecdotes, First Evidence

Ingestion of the plant *Cannabis sativa* L., i.e., marijuana smoking or hashish ingestion, has long been reported to increase hunger and appetite. Because marijuana ingestion often was followed by a special craving for sweets, one of the first modern investigations (1942) of this topic concluded that cannabis stimulates appetite by lowering blood glucose.[20] However, it has been well documented that neither smoked marijuana nor orally ingested THC has any significant effect on plasma glucose levels.[20,36]

A double-blind placebo-controlled study with healthy male volunteers living continuously in a residential laboratory demonstrated that smoked marijuana versus placebo cigarettes increased the mean daily caloric intake by 20 percent.[16] Another trial in the same setting showed that marijuana significantly increased food intake for 40 percent compared to placebo.[15] Body weight increased 3 kg on average over the three-day active marijuana period. This was an increase in body weight greater than predicted by the increase in caloric intake. It could not be confirmed that this phenomenon also described by other investigators, would be a consequence of increased fluid retention, i.e., no changes in urinary or plasma fluid volume were associated with marijuana consumption (summarized by Foltin et al.[15]).

Mechanism of Action

A molecular basis has been provided for the pharmacological actions of cannabis and its cannabinoids through the discovery of cannabinoid receptors and endogenous cannabinoids, called anandamides (see Chapter 7).

The central cannabinoid system may play an important role as well in appetite regulation. Several animal models have shown that specific cannabinoid receptor-related processes are involved in the central control of eating behavior, demonstrating hyperphagic effects of Δ^9-THC and anandamides, and hypophagic actions of selective cannabinoid receptor antagonists. As an example, in male rats a significant overeating was induced by subcutaneous injections of anandamide, this effect was dose-dependent attenuated by pretreatment with a specific cannabinoid$_1$ receptor-antagonist.[38]

Δ^9-THC and Cannabis Extracts for Clinical Use

Delta-9-tetrahydrocannabinol (dronabinol, THC), the major psychoactive component of *Cannabis sativa,* was first used therapeutically as an antiemetic and is available by prescription in several countries (Marinol). Growing evidence suggests that other cannabinoids contribute to the therapeutic effects of THC (see Chapter 5) and trials with standardized cannabis preparations are underway or being prepared.

Cancer Cachexia

A phase I study with oral THC in 10 advanced cancer patients showed no side effects at a low dose level (0.1 mg/kg per day). Two of three patients at an intermediate dose (0.18 mg/kg per day) and three of four patients at high-dose (0.34 mg/kg per day) experienced somnolence, dizziness, and a feeling of "drunkenness."[32]

For the following double-blind, crossover phase II study (two one-week treatment periods) in 54 advanced cancer patients 0.1 mg oral THC/kg t.i.d. was given. Only 6/20 patients left the trial because of side effects in the THC-week (dizziness, confused thinking, panic reaction). Patients treated with THC showed significantly less depression, improved emotional stability, and reduction of inner tension, without experience of euphoria or "high." No patient had any previous contact with cannabis, and they were told the drug given was a "tonic" to stimulate appetite, not telling them its relation to "marijuana." In the study, 16/34 patients were evaluable for weight change (no third-space fluid accumulation) and showed a significant weight gain during THC (+0.69 kg THC first/+0.39 kg placebo first) compared to placebo period (–2.1 kg/–1.1 kg).[32]

In an open, dose-ranging pilot study, 42 cancer patients (some treated with chemotherapy) received Marinol (THC) 2.5 or 5 mg once daily (q.d.), or 2.5 or 5 mg twice daily (b.i.d.) for six weeks. Ten patients terminated the study early because of side effects (dizziness, memory and mood changes), only one of these patients were in the 2.5 mg q.d and b.i.d group, respectively. A significant 47 percent increase over baseline of appetite (VAS) in the 2.5 mg b.i.d. group was shown. Overall, no group showed a significant weight gain. However, there was a significant reduction in weight loss for the 2.5 mg q.d. and 5 mg q.d. groups, but demonstrating no clear dose-effect relationship.[31]

Nineteen advanced cancer patients suffering from anorexia were treated in an open-label phase II study with THC 2.5 mg p.o. t.i.d. for 4 weeks. Four patients terminated early because of side effects and 13/18 evaluable patients reported an improved appetite.[27]

No published phase III trials of dronabinol or cannabis extracts in patients with advanced cancer are currently available. In November 1999, the

authors, together with Thomas Cerny as third investigator started a phase III trial comparing the efficacy of THC standardized cannabis extract and dronabinol on anorexia-cachexia in cancer patients in Germany and Switzerland.

AIDS Wasting

The open trials in cancer patients provided the basis for the dronabinol doses selected for studies in AIDS patients. Two small studies of dronabinol in HIV-infected patients demonstrated a trend toward enhanced appetite and mood, and weight stabilization.[18,34]

Beal and colleagues[2] conducted a randomized, placebo-controlled, double-blind study in AIDS patients who had to have lost at least 2.5 kg from their normal body weight. Seventy-two patients received dronabinol 2.5 mg orally twice a day and 67 patients received placebo, for a duration of six weeks. Of the evaluable patients (i.e., 63 percent), 38 percent noted an increase in appetite versus 8 percent of the placebo group after two weeks of treatment. This difference was statistically significant. Nausea was improved in dronabinol-treated patients by 22 percent compared to 4 percent in the placebo group. An increase in body weight was not statistically significant.

After this blinded trial,[2] an open-label follow-up study was carried out, in which 94 patients who completed the six weeks treatment with dronabinol or placebo were treated with dronabinol twice daily (titration of the dose between 2.5 mg and 20 mg THC/d). Of these patients, 24 percent completed the full 12-month course of treatment, with the primary reason for early termination being intercurrent illness and drug toxicity. The increase in appetite experienced after dronabinol treatment in the first trial was sustained for the 12-month duration and patients did not develop tolerance to the appetite-stimulating effect. Of all these patients, 25 percent achieved a weight gain of 2 kg or more during the 12-month period.[3]

In both trials[2,3] adverse effects were related to the central nervous system: anxiety, confusion, dizziness, euphoria, somnolence, or thinking abnormalities occurred in up to 38 percent of the patients. There was no evidence of drug interactions between dronabinol, retroviral medicines, and other medication used to treat HIV infection.

In a randomized, open-label trial comparing safety and pharmacokinetics of dronabinol with and without megestrol acetate (treatment of 12 weeks duration) 52 AIDS patients with wasting syndrome were randomized into four treatment arms: dronabinol (D) 2.5 mg twice daily (result: no weight gain), megestrol acetate (MA) 750 mg/d (6.5 kg weight gain), MA 750 mg plus D 2.5 mg twice a day (6 kg weight gain), and MA 250 mg plus D 2.5 mg twice daily (no weight gain).[35]

Although THC has been shown to increase appetite with trends toward weight stabilization in AIDS patients, it remains to be established in controlled trials if there would be any additive effects to the use of standardized cannabis extracts in the management of AIDS wasting.

CONCLUSION

In the management of anorexia-cachexia in cancer and AIDS wasting there is growing evidence that patients need individual treatment, according to the main underlying metabolic abnormalities and accompanying symptoms. In this view, cannabinoids such as THC or standardized cannabis extracts might prove useful, either as single drugs or in combination with other drugs, in the palliative treatment of those patients with symptoms such as anorexia, chronic nausea, asthenia, and depression.

Clearly, there is a strong need for randomized, double-blind, placebo-controlled clinical trials with accurate, defined outcome parameters which focus on the symptomatic and quality-of-life advantages to determine the safety, efficacy, and usefulness of THC and/or *Cannabis sativa* (in the form of standardized pharmaceutical preparations) in patients with anorexia and cachexia.

REFERENCES

1. Abbaticola M, Fisher AE. Viral load response to HAART is an unpredictable indicator of BCM anabolism or catabolism. *12th World AIDS Conference*. Geneva July 1998, Abstract Book, No. 60517.

2. Beal JE, Olson R, Laubenstein L, Morales JP, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management* 1995;10(2):89-97.

3. Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 1997;14(1):7-14.

4. Billingsley KG, Alexander HR. The pathophysiology of cachexia in advanced cancer and AIDS. In Bruera E, Higginson I, eds. *Cachexia-Anorexia in Cancer Patients*. Oxford: Oxford Medical Publications, Oxford University Press 1996;1:1-22.

5. Body JJ. The syndrome of anorexia-cachexia. *Current Opinion in Oncology* 1999;11(4):255-260.

6. Bozzetti F, Amadori D, Bruera E, Cozzaglio L, Corli O, Filiberti A, Rapin CH, Neuenschwander H, Aoun M, Ricci SB, et al. Guidelines on artificial nutrition

versus hydration in terminal cancer patients. European Association for Palliative Care. *Nutrition* 1996;12(3):163-167.

7. Bruera E, MacDonald RN. Nutrition in cancer patients: An update and review of our experience. Issues in symptom control. Part 3. *Journal of Pain and Symptom Management* 1988;3(3):133-140.

8. Bruera E, Fainsinger RL. Clinical Managment of cachexia and anorexia. In Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Textbook of Palliative Medicine,* Second Edition. New York: Oxford University Press; 1998; 548-557.

9. Bruera E, Higginson I. Preface. In Bruera E, Higginson I, eds. *Cachexia-Anorexia in Cancer Patients*. Oxford: Oxford Medical Publications, Oxford University Press, 1996, pp. v-vi.

10. Bruera E, Neumann CM, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer: Preliminary report. *Annals of Oncology* 1999;10(7):857-859.

11. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998;351 (9119):1881-1883.

12. Coodley GO, Loveless MO, Merrill TM. The HIV wasting syndrome: A review. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1994;7(7):681-694.

13. Corcoran C, Grinspoon S. Treatments for wasting in patients with the acquired immunodeficiency syndrome. *New England Journal of Medicine* 1999; 340(22):1740-1750.

14. DeWys WD, Begg C, Lavin PT, Bennett JM, Bertino JR, Cohen MH, Douglass Jr HD, Engstrom PF, Ezdinlie Z, Horton J, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *American Journal of Medicine* 1980;69(4):491-497.

15. Foltin RW, Fischman MW, Byrne MF. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 1988;11(1):1-14.

16. Foltin RW, Fishman MW, Brady JV. Behavioral analysis of marijuana effects on food intake in humans. *Pharmacology, Biochemistry and Behavior* 1986; 25(3):577-582.

17. Gagnon B, Bruera E. A review of the drug treatment of cachexia associated with cancer. *Drugs* 1998;55(5):675-688.

18. Gorter R, Seefried M, Volberding P. Dronabinol effects on weight in patients with HIV infection. *AIDS* 1992;6(1):127.

19. Hellerstein MK, Wu K, McGrath M, Faix D, George D, Shackleton CH, Horn W, Hoh R, Neese RA. Effects of dietary n-3 fatty acid supplementation in men with weight loss associated with the acquired immune deficiency syndrome: Relation to indices of cytokine production. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1996;11(3):258-270.

20. Hollister LE. Hunger and appetite after single doses of marijuana, alcohol and dextroamphetamine. *Clinical Pharmacology and Therapeutics* 1971;12(1):44-49.

21. Jaskowiak NT, Alexander HR. The pathophysiology of cancer cachexia. In Doyle D, Hanks GWC, MacDonald N, eds. *Oxford Textbook of Palliative Medicine,* Second Edition. New York: Oxford University Press; 1998, 534-548.

22. Khan S, Tisdale MJ. Catabolism of adipose tissue by a tumour-produced lipid-mobilising factor. *International Journal of Cancer* 1999;80(3):444-447.

23. Laviano A, Meguid MM. Nutritional issues in cancer management. *Nutrition* 1996;12(5):358-371.

24. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, Rowland Jr KM, Camoriano JK, Novotny PJ, Christensen BJ. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *Journal of Clinical Oncology* 1999;17(10):3299-3306.

25. Lorite MJ, Thompson MG, Drake JL, Carling G, Tisdale MJ. Mechanism of muscle protein degradation induced by a cancer cachectic factor. *British Journal of Cancer* 1998;78(7):850-856.

26. Mantovani G, Maccio A, Lai P, Massa E, Ghiani M, Santona MC. Cytokine activity in cancer-related anorexia/cachexia: Role of megestrol acetate and medroxyprogesterone acetate. *Seminars in Oncology* 1998;25(2 Suppl 6):45-52.

27. Nelson K, Walsh D, Deeter P, Sheehan F. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. *Journal of Palliative Care* 1994;10(1):14-18.

28. Ottery FD, Walsh D, Strawford A. Pharmacologic management of anorexia/cachexia. *Seminars in Oncology* 1998;25(Suppl 6):35-44.

29. Padilla GV. Psychological aspects of nutrition and cancer. *Surgical Clinics of North America* 1986;66(6):1121-1135.

30. Palenicek JP, Graham NM, He YD, Hoover DA, Oishi JS, Kingsley L, Saah AJ. Weight loss prior to clinical AIDS as a predictor of survival. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1995;10(3):366-373.

31. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacology, Biochemistry and Behavior* 1991;40(3):695-700.

32. Regelson W, Butler JR, Schulz J, Kirk T, Peek L, Green ML, Zalis MO. Tetrahydrocannbinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In Braude MC, Szara S, eds. *The pharmacology of marihuana.* A Monograph of the National Institute of Drug Abuse. New York: Raven, 1976;763-776.

33. Sherry BA, Gelin J, Fong Y, Marano M, Wei H, Cerami A, Lowry SF, Lundholm KG, Moldawer LL. Anticachectin/tumor necrosis factor-alpha antibodies attenuate development of cachexia in tumor models. *FASEB Journal* 1989; 3(8):1956-1962.

34. Struwe M, Kaempfer SH, Geiger CJ, Pavia AT, Plasse TF, Shepard KV, Ries K, Evans TG. Effect of dronabinol on nutritional status in HIV infection. *Annals of Pharmacotherapy* 1993;27:827-831.

35. Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G, and the DATRI 004 Study Group. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Research and Human Retroviruses* 1997;13(4):305-315.

36. Weil AT, Zinberg NE, Nelson JM. Clinical and psychological effects of marijuana in man. *Science* 1968;162(859):1234-1242.

37. Wigmore SJ, Ross JA, Falconer JS, Plester CE, Tisdale MJ, Carter DC, Fearon KC. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. *Nutrition* 1996;12(Suppl 1):27S-30S.

38. Williams CM, Kirkham TC. Anandamide induces overeating: Mediation by central cannabinoid (CB_1) receptors. *Psychopharmacology* 1999;143(3):315-317.

Chapter 14

Antiemetic Effects of Cannabinoids

Terry Plasse

Nausea and vomiting are symptoms caused by a wide variety of stimuli, such as diseases of the gastrointestinal tract, central nervous system and inner ear, metabolic abnormalities, and a wide variety of drugs. Prominent among the last category are cytotoxic agents used in cancer chemotherapy. Generally, nausea accompanies vomiting and appears to be a lower level stimulation of the vomiting reflex. There are, however, situations, such as intestinal obstruction, in which vomiting may occur in the absence of nausea. In addition to a variety of pathologic and pharmacologic processes and stimuli, nausea and vomiting may be initiated by psychologic factors, such as associations with unpleasant odors or events. A classic example of the latter, anticipatory vomiting, is the cancer chemotherapy patient who begins to vomit upon arrival at the doctor's office or on seeing personnel associated with previous administration of chemotherapy.

Nausea and vomiting are controlled by the vomiting center in the medulla;[21] (this chapter provides references to many of the primary sources for the pathophysiology of emesis). Input to the vomiting center comes from several sources. The vagus and sympathetic nerves from the gastrointestinal tract may stimulate vomiting. The vestibular apparatus sends impulses via the cerebellum. (This source is important in nausea related to inner ear disorders as well as in motion sickness.) Cortical sources are also presumably involved. Much of the emetogenicity of cancer chemotherapy appears to be related to effects on the chemoreceptor trigger zone (CTZ), an area on the upper surface of the medulla from which neurons pass into the vomiting center.

In certain situations pharmacologic treatment of vomiting is contraindicated. For example, patients with possible intestinal obstruction should undergo therapy to either relieve the obstruction or allow decompression of the gut, i.e., gastrointestinal drainage. Often, however, there is no specific ther-

apy for the condition causing emesis, and symptomatic treatment is the only way to relieve the problem. Acute labyrinthitis, self-limited viral syndromes, and cytotoxic chemotherapy-induced emesis are among the latter.

ANTIEMETICS IN CLINICAL USE

The large number of antiemetics agents available reflects the diversity of etiologies and pathways involved in emesis. Among the earliest agents used were antihistamines and phenothiazines. Antihistamines have been used primarily for control of nausea and vomiting associated with inner ear disease; H_2 receptors are present in the vestibular nucleus.[30] Phenothiazines, at doses below those used for control of psychosis, are often used for treatment of nausea and vomiting due to acute viral illnesses and cytotoxic chemotherapy. They block dopamine D_2-receptors in the CTZ[31] and increase lower esophageal sphincter pressure.[4] They are moderately effective, but often cause unpleasant side effects, particularly extrapyramidal symptoms.

Corticosteroids, benzodiazepines, and metoclopramide are all used as antiemetics against chemotherapy-induced emesis. They act upon a variety of different pathways. Therefore, combining them with each other and with phenothiazines or 5-HT_3 antagonists, is pharmacologically rational and clinically has been shown to enhance activity as compared to single-agent therapy.[21,22]

In the early 1990s, several 5-HT_3 (serotonin) antagonists were shown to be highly active in controlling cytotoxic-induced emesis.[22] Several of these compounds are now available clinically. As single agents, they are far more active than other classes of drugs against highly emetogenic cytotoxics such as cisplatin. In addition, side effects are uncommon and generally mild. In combination with other drugs, especially corticosteroids, they are now the mainstay of antiemetics therapy for cancer chemotherapy patients.

RATIONALE FOR THE USE OF CANNABINOIDS AS ANTIEMETICS

The study of cannabinoids as antiemetics was prompted by anecdotal observations that smoking marijuana prior to cytotoxic chemotherapy decreased nausea and vomiting.[27] A more recent study has shown that cannabinoid agonists inhibit activation of 5-HT_3 receptors in a rat model.[10] This provides a rationale and possible mechanism of action for the empirically observed antiemetic activity.

Delta-9-tetrahydrocannabinol (Δ^9-THC, dronabinol) is the most thoroughly studied cannabinoid, and is currently approved in the United States as an antiemetic for patients receiving cancer chemotherapy, as well as for enhancement of appetite in AIDS patients.

CLINICAL DATA

In the late 1970s, several studies either against placebo or prochlorperazine demonstrated the antiemetic activity of dronabinol in patients receiving anticancer chemotherapy. Table 14.1 shows the results of blinded studies comparing dronabinol to placebo; in two of the five studies listed, prochlorperazine was also tested. The patient populations and definitions of response varied from study to study, and in some studies statistical comparisons were not given. The results overall, however, clearly demonstrate that oral dronabinol is an active antiemetic for patients receiving cancer chemotherapy. The dose of dronabinol used ranged from 7 to 10 mg/m^2 given every 4 hours (q4h), usually starting a few hours prior to and continuing until the completion of chemotherapy. Side effects were common among patients receiving dronabinol, and consisted of effects generally ascribed to marijuana: euphoria, dizziness, sedation, and hypotension. Some patients reported hallucinations and unpleasant, frightened feelings. In one study,[16] although significant antiemetic activity was demonstrated, side effects were felt to outweigh the benefit of treatment.

Table 14.2 shows the results of studies comparing dronabinol to other antiemetics, most commonly prochlorperazine. The 5-HT_3 antagonists were introduced after these studies, and controlled comparisons between this class of agents and dronabinol are lacking. The blinded studies listed in the tables show dronabinol to be as active (four studies) or better (four studies) than a phenothiazine; in seven of the eight studies, the comparator was prochlorperazine. Two studies compared dronabinol with metoclopramide. In one, with oral metoclopramide given at a relatively low dose to pediatric patients, dronabinol was superior. In the other, high dose intravenous metoclopramide was given to adult patients receiving cisplatin-containing chemotherapeutic regimens, which are more emetogenic than most other types of chemotherapy. In the second study, intravenous metoclopramide was more effective and caused fewer side effects than oral dronabinol.

Table 14.3 shows results of two studies in which dronabinol was given in combination with prochlorperazine. In both, the combination was more effective than prochlorperazine alone. In addition, in one study,[17] the incidence of cannabinoid-induced adverse effects was decreased when the drug was combined with prochlorperazine, which has antipsychotic as well as antiemetic effects. Thus, it appears that the combination of dronabinol and prochlorperazine, a commonly used antiemetic, is not only more effective than either drug but is better tolerated than dronabinol alone.

Other cannabinoids, including crude marijuana, have been used as antiemetics. As noted earlier, the impetus for studying cannabinoids as antiemetics came from anecdotal observations of the antiemetic activity of smoked marijuana. However, very little controlled work has been done to

TABLE 14.1. Antiemetic Activity of Oral Dronabinol Compared to Placebo

Study Design	Regimen	Response Criteria	Response to Dronabinol	Response to Placebo	Comments/ Reference
Double-blind, placebo control cross-over in patients receiving moderately emetogenic regimens; 22 patients had received prior chemotherapy; 2 chemotherapy naive	15 mg or 10 mg/m^2 q4h × 3 doses; either active or matching placebo	CR=no vomiting; PR=50% decrease in number of episodes of vomiting from previous course	5 CR, 7 PR/15 courses	0 responses/ 14 courses	Sallan et al.[27]
Double-blind, placebo control cross-over administered on days 1 and 8 to patients (age 21 to 53, median 32 years) receiving MOPP chemotherapy	10 mg/m^2 q4h × 3 doses; either active or matching placebo	Scale of 1 (no improvement) to 5 (complete inhibition of emesis) as compared to prior cycles of chemotherapy	Day 1 mean 2.27 ± 1.03; day 8 mean 3.93 ± 1.33	Day 1 mean 1.09 ± 0.30; day 8 mean 1.67 ± 0.89 P <. 01 for difference between groups at days 1 and 8 independently	P<.01 for difference between groups at days 1 and 8 independently Kluin-Nelemans et al.[16]
Double-blind, parallel group trial in gastrointestinal malignancy patients (>21 years old) receiving methyl CCNU and 5-fluorouracil +vincristine, doxorubicin, razoxane or triazinate	15 mg, prochlorperazine 10 mg or placebo 2 hr before chemo, 2 and 8 hr after chemo	Day 1: strong emetic stimulus: No nausea (N) or vomiting (V) vs N only vs N and V Days 2 through 4: weak emetic stimulus: same parameters	Day 1 (N = 38) Percent with No N or V 42 N only 5 and V 53	Day 1: Placebo (N = 37) Percent with No N or V 19 N only 16 N and V 65 Prochlorperazine (N = 41) Percent with No N or V 42 N only 2 N and V 56	Day 1: p <. 05 among 3 groups, but no difference between prochlorperazine or THC; days 2 through 4: no significant difference among groups Frytak et al.[13]

Single-blind, placebo control crossover trial in patients receiving high dose methotrexate for osteogenic sarcoma	Dronabinol 10 mg/m^2 q3h × 5 doses starting 2 h before each of 6 cycles of chemotherapy; supplementation with extracted marijuana cigarette loaded with THC (or placebo) for patients experiencing vomiting on previous cycle	Response based on episodes of vomiting, severity of nausea, duration of nausea and volume of oral intake; graded excellent (>80% decrease for all variables on THC compared to placebo), fair (30 to 80% reduction of >3 variables) or none (<30% reduction of >2 variables)	Of 15 patients, 8 (53%) excellent; 6 (40%) fair; 1 (7%) no response; Significant ($p < .02$) reductions in vomiting episodes and volume, duration and severity of nausea		Chang et al.[5]
Double-blind, crossover trial against placebo and prochlorperazine in patients who had failed other antiemetics	7 mg/m^2 of either dronabinol or prochlorperazine or placebo given every 4 h for 4 doses beginning 1 h before chemotherapy	Complete response: no nausea or vomiting	40/55 (73%) of courses	8/55 (15%) of prochlorperazine courses; 5/55 (9%) of placebo courses	Orr et al.[24]

TABLE 14.2. Antiemetic Activity of Oral Dronabinol Compared to Active Controls

Study Design	Regimen	Response Criteria	Response, Dronabinol	Response, comparator	Comments/ Reference
Double-blind, active control crossover in pediatric patients (ages 5 to19, median 11 years) receiving moderately emetogenic chemotherapy	Dronabinol 10 mg/m^2 (maximum 15 mg) 2 hr prior to chemo and 4, 8, 16 and 24 h after the first dose; prochlorperazine 5 to 10 mg per dose depending on BSA; placebo at 4 h after first dose	Number of patients with nausea, anorexia, and number of episodes of vomiting	18 cycles: Nausea 6 Vomiting: 0 9 1-6 9 >6 0 Anorexia 1	18 cycles: Nausea 18 Vomiting: 0 0 1-6 14 >6 4 Anorexia 4	P <.001 for nausea, vomiting; NS for anorexia Ekert et al.[9]
Double-blind, parallel group trial in gastrointestinal malignancy patients (>21 years old) receiving methyl CCNU and 5-fluorouracil +vincristine, doxorubicin, razoxane or triazinate	Dronabinol 15 mg, prochlorperazine 10 mg or placebo 2 hr before chemo, 2 and 8 h after chemo	Day 1: strong emetic stimulus: No nausea (N) or vomiting (V) vs N only vs N and V Days 2 through 4: weak emetic stimulus: same parameters	Day 1 (N = 38) Percent with No N or V 42 N only 5 N and V 53	Day 1: Placebo (N = 37) Percent with No N or V 19 N only 16 N and V 65 Prochlorperazine (N = 41) Percent with No N or V 42 N only 2 N and V 56	Day 1: p <.05 among 3 groups, but no difference between prochlorperazine or THC; days 2 through 4: no significant difference among groups Frytak et al.[13]
Double-blind, crossover trial comparison against prochlorperazine in patients receiving various chemotherapy regimens, mean age 32.5 years (9 to 70)	Dronabinol 10 mg/m^2 (maximum 15 mg) vs prochlorperazine 10 mg, either given 1 h before, 3 and 7 h after chemotherapy	Complete response: no nausea or vomiting	36/79 (46%) of courses	16/78 (21%) of courses	Significance between complete response rates not given Sallan et al.[26]

Double-blind, crossover trial against placebo and prochlorperazine in patients who had failed other antiemetics	7 mg/m^2 of either dronabinol or prochlorperazine given q4h for 4 doses beginning 1 h before chemotherapy	Complete response: no nausea or vomiting	40/55 (73%) of courses	8/55 (15%) of prochlorperazine courses; 5/55 (9%) of placebo courses	Orr et al.[24]
Double-blind, crossover trial against thiethylperazine or metoclopramide in 35 patients receiving various chemotherapeutic agents	Dronabinol 12.12 mg/m^2 or thiethylperazine 6.67 mg/m^2 orally or metoclopramide 4.55 mg/m^2 iv 2 h before and 2 and 6 h after chemotherapy	Overall severity of nausea and vomiting (0-5), number of episodes of vomiting	Mean severity 0.86 ± 0.19; mean episodes of vomiting 2.70 ± 0.74	For metoclopramide: severity 0.59 ± 0.17; episodes 1.98 ± 0.75; for thiethylperazine severity 0.92 ± 0.19, episodes 2.39 ± 0.61	Differences not significant Colls et al.[7]
Parallel group study of patients receiving antiemetics for first course of chemotherapy	Dronabinol either 5, 10, or 15 mg, prochlorperazine 10 mg or placebo 2 h before and 2, 6, and 10 h after start of chemotherapy	Ranking by research nurse of overall antinauseant and control of vomiting	THC 15 mg was the most effective against vomiting	Prochlorperazine was the most effective antinauseant	Relatively large study, but responses poorly described. Levitt et al.[19]
Double-blind, crossover trial in 214 patients receiving either single day or multiple day chemotherapeutic regimens; 75% had previously received prochlorperazine	Dronabinol 7.5 mg for BSAa < 1.4 m^2; 10 mg for BSA 1.4-1.8 m^2; 12.5 mg for BSA>1.8 m^2 or prochlorperazine 10 mg fixed dose q4h ×4 doses starting 1 h before chemotherapy	Graded 0-6: no nausea or vomiting through multiple episodes of vomiting	No significant differences over time between treatments for either single day or multiple day regimens; both drugs were effective		Ungerleider et al.[28]

TABLE 14.2 *(continued)*

Double-blind, crossover trial in patients refractory to other antiemetics	Dronabinol 15 mg/m^2 vs prochlorperazine 10 mg, either given 1 h before chemotherapy and q4h thereafter for 24 h	Complete absence of nausea and vomiting	9/36 (25%) complete response	1/36 (3%) complete response	McCabe et al.[20]
Double-blind, active control crossover in pediatric patients (ages 5 to 19, median 11 years) receiving moderately emetogenic chemotherapy	Dronabinol 10 mg/m^2 (maximum 15 mg) 2 hr prior to chemo and 4, 8, 16, and 24 after the first dose; metoclopramide 10 mg for patients with BSA > 0.7 m^2; 5 mg for those with BSA < 0.7 m^2; (4 hr dose placebo); matched, double-dummy controls	Number of patients with nausea, anorexia, and number of episodes of vomiting	17 cycles: Nausea 6 Vomiting: 0 12 1-6 3 >6 2 Anorexia 4	25 cycles: Nausea 21 Vomiting: 0 5 1-6 6 >6 12 Anorexia 16	P <. 01 for nausea, vomiting; <.05 for anorexia Ekert et al.[9]
Double-blind, double dummy parallel group trial in patients (ages 39 to 72, median 58 years) receiving cisplatin-containing chemotherapy regimens	Dronabinol 10 mg/m2 1.5 h prior to chemotherapy, then q3h for a total of 5 doses; metoclopramide 2 mg/kg iv 0.5 h prior to chemotherapy then q2h for a total of 5 doses	Number of episodes and volume of emesis; duration of nausea and vomiting; major antiemetic control defined as <2 vomiting episodes	Median emetic episodes 3; major antiemetic control 4/15 (27%) of patients	Median emetic episodes 2; major antiemetic control 11/15 (73%) of patients	P = .02 for emetic episodes; .01 for percent patients with major antiemetic control; also trends favoring metoclopramide for volume of emesis and duration of vomiting Gralla et al.[14]

TABLE 14.3. Antiemetic Activity of Oral Dronabinol Added to Prochlorperazine

Study Design	Regimen	Response Criteria	Response	Comments/ Reference
Double-blind, crossover in patients (median age 42, range 16 to 80 years) receiving various chemotherapies and refractory to previous antiemetics therapy	Dronabinol 5 mg/m^2 vs placebo; all patients received prochlorperazine 10 mg; both drugs given q6h starting 24 to 48 prior to and following chemotherapy or radiotherapy	Degree of control, described as none, moderate or excellent; terms not defined	18/20 (90%) patients receiving combination had moderate-excellent relief as compared to prior antiemetics. 3/20 (15%) patients receiving placebo plus prochlorperazine had moderate to excellent relief; $p < .001$	Only first course analyzable; drop-out rate too high to analyze crossover. Artim and DiBella[3]
Double-blind, parallel group in patients (median age 52, range 20 to 68 years) in patients receiving various chemotherapeutic regimens	Dronabinol 10 mg plus placebo versus prochlorperazine 10 mg plus placebo versus the combination every 6 h starting 24 h prior to chemotherapy and continuing until 24 h after the last dose	Number of episodes of nausea, vomiting, severity of nausea by visual analogue scale	Trend towards more patients without nausea alone, vomiting alone, and nausea or vomiting with combination > dronabinol > prochlorperazine alone. Duration of episodes of nausea or vomiting less with combination than with either dronabinol or prochlorperazine; trend towards shorter episodes with dronabinol as compared to prochlorperazine. Nausea significantly less severe with combination than with either dronabinol or prochlorperazine.	Lane, et al.[17]

elucidate the relative benefits and disadvantages of smoked marijuana as compared to oral administration of the major active component. This lack of information does give both sides in the ongoing political debate the opportunity to argue their points unencumbered by data.

An open study of marijuana as an antiemetic was performed with 56 patients at least 18 years of age and who were refractory to standard antiemetic agents.[29] Patients smoked a marijuana cigarette 6 to 8 h prior to chemotherapy and then every 4 to 6 h after for a total dose of 4 cigarettes per day on chemotherapy; each dose of dronabinol administered was 5 mg/m^2. Eighteen patients (34 percent) rated marijuana very effective, and 26 (44 percent) rated it moderately effective, for an overall response rate of 78 percent. The meaning of very or moderately effective was not defined. This response rate is similar to the 80 percent complete and partial response rate found by Sallan and colleagues for oral THC.[27] In a crossover, double-blind study comparing oral and inhaled THC (capsules versus marijuana, see Table 14.4), no significant difference in antiemetic control was found.[18] Adverse effects occurred at similar frequency with both treatments.

Table 14.4 also shows the results of several studies with other cannabinoids. Several synthetic cannabinoids have been synthesized and undergone clinical testing. Patients receiving intramuscular levonantradol had fewer episodes of vomiting than those receiving oral dronabinol ($p = .06$).[6] Nabilone was found to be more active than prochlorperazine in two studies and than domperidone in two studies; all medications were given orally. Psychotropic effects occurred occasionally with the cannabinoids in all of these studies.

An additional natural cannabinoid, Δ^8-THC, has also been tested as an antiemetic.[1] This compound may be less psychoactive than the more commonly used isomer, dronabinol. In an open study, Δ^8-THC 18 mg/m^2 per 05 q6h for 24 h was administered as oral drops to eight pediatric patients (ages 3.5 to 10 years) receiving cancer chemotherapy. No vomiting occurred during study drug administration; most patients received multiple courses of the antiemetic. Side effects were milder than would have been expected for the same dose of dronabinol. In a previous study, Δ^8-THC had been found to be 25 percent less potent psychotropically than dronabinol.[15] In addition, baby mice were found to be resistant to the motor effects of anandamide and dronabinol, whereas weanling mice were affected.[12] The implication of this last study is that young animals do not have the psychotropic reactions that adults do. Both the lower psychotropic potency of Δ^8-THC and the fact that young patients may be less sensitive to the psychotropic effects of all cannabinoids than adults may explain why pediatric patients tolerated Δ^8-THC as well as they did.

A synthetic cannabinoid, a dimethylheptyl homologue of 7-hydroxy-delta-6-tetrahydrocannabinol (HU-211), has been found in animal models

TABLE 14.4. Antiemetic Activity of Other Cannabinoids

Study design	Regimen	Response Criteria	Results	Comments/ Reference
Double-blind, double dummy crossover in 20 chemotherapy-naive patients, ages 28 to 78 (mean 54.5) years	Oral dronabinol 15 mg po or marijuana cigarette q4h starting 2 h before chemotherapy	Preference for agent	9 patients no preference (5 treatment failures, 4 equivalent efficacy); 7 preferred oral THC, 4 preferred marijuana cigarettes	No significant differences Levitt et al.[18]
Double-blind, double dummy crossover in adults	Levonantradol 1 mg im or dronabinol 15 mg po q4h ×7 doses starting 2 h before chemotherapy; 46 patients entered; analysis only on 26 patients who completed crossover	Number of episodes of emesis; severity of nausea and vomiting graded as 1 = none; 2 = mild, not interfering with activity; 3 = severe, causing intense distress, bedridden for >2 h	Levonantradol: mean/median number of episodes of emesis: 2.9/2.0; severity: 1: 28%; 2: 60%; 3: 12% Dronabinol: mean/median number of episodes of emesis: 5.0/3.0; severity: 1: 28%; 2: 52%; 3: 20%	P = .06 for median number of episodes of emesis; not given for severity Citron et al.[6]
Double-blind, double dummy crossover in lung cancer patients, median age 58 years (range 27 to 72) 34 patients entered, 28 evaluable	Nabilone 2 mg po q12h × 3 days or prochlorperazine 10 mg po q8h x 3 days; rescue metoclopramide or chlorpromazine as needed	Symptom questionnaire covering anorexia, nausea, retching and vomiting graded 0-3 for each symptom	Significantly less of each symptom on at least 1 of 3 days evaluated. Both treatments well tolerated	Ahmedzai et al.[2]

TABLE 14.4 *(continued)*

Double-blind, crossover study in lung cancer patients, mean age 61 years (range 48 to 78); 32 entered, 24 evaluable in crossover	Nabilone 2 mg po q12h or prochlorperazine 15 mg po q12h, starting 1 h before chemotherapy and continuing 24 h after last dose	Nausea, vomiting and appetite were assessed by the patient and by the investigators; number of episodes of emesis over first 24 h of chemotherapy	Median episodes of vomiting 6.5 with nabilone, 11 with prochlorperazine ($p < .05$); no significant differences in nausea, appetite or investigators' global assessment. 16 patients (67%) preferred nabilone, 6 (25%) prochlorperazine; 2 (8%) no preference ($p = .05$). 15/27 (55%) patients reported adverse effects with nabilone, 3 (11%) severe; 1/27 (4%) patients reported adverse effects, mild asthenia, after prochlorperazine.	Niiranen and Mattson[23]
Double-blind, crossover study in adults (mean age 42 years, range 21 to 66) receiving chemotherapy ; 38 patients entered, 31 completed crossover; all cycles analyzed	Nabilone 1 mg po tid or domperidone 20 mg po, starting the night before chemotherapy and continued q8h each day of chemotherapy	Number of episodes of vomiting; severity of nausea and food intake	Mean episodes of vomiting 4.53/cycle for nabilone, 10.81 for domperidone ($p <. 01$); no significant difference for nausea or appetite. No hallucinations noted; dizziness and postural hypotension more common with nabilone; drowsiness similar	Pomeroy et al.[25]

Double-blind, crossover study in children (age range 0.8 to 17 years); 23 entered, 18 completed crossover	Nabilone: <18 kg: 0.5 mg q12h; 18-36 kg: 1 mg q 12h; >36 kg: 1 mg q8h; domperidone: <18 kg: 5 mg; 18-36 kg: 10 mg; >36 kg 15 mg, all q8h	Number of episodes of vomiting; severity of nausea (0-3), study drug preference	Nabilone Domperidone P Episodes vomiting 5.94 16.72 <.01 Severity of nausea 1.50 2.50 .01 Preference 12 1 <.01 Adverse effects more common with nabilone, but only one patient, who hallucinated, found them unacceptable	Dalzell et al.[8]

to be a potent antiemetic but devoid of psychotropic activity.[11] It is currently in clinical testing for other indications (see Chapter 36). It might, if used as an antiemetic, have a markedly improved therapeutic ratio as compared to other cannabinoids.

CURRENT ROLE OF CANNABINOIDS AS ANTIEMETICS

At present, the only approved natural cannabinoid is dronabinol. In addition, the synthetic THC derivate, nabilone, is available for this indication in some countries. The use of combination antiemetics is the rule, and combining dronabinol with prochlorperazine has been shown to improve antiemetic efficacy while reducing cannabinoid side effects. Dronabinol is not heavily used, however, because more potent antiemetics with fewer side effects, the 5-HT_3 antagonists, are available. None of the other cannabinoids tested has been shown to have a markedly better therapeutic index than dronabinol.

An area that could be explored, and one which may not be as well controlled by 5-HT_3 antagonists as acute emesis, is delayed emesis over the several days after chemotherapy. Although controlled studies have not been carried out, anecdotal reports have suggested a role for dronabinol for this indication. Newer analogues, such as HU-211, may also offer improved efficacy with fewer side effects.

REFERENCES

1. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sciences* 1995;56(23-24):2097-2102.

2. Ahmedzai S, Carlyle DL, Clader IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *British Journal of Cancer* 1983;48(5):657-663.

3. Artim R, DiBella N. Tetrahydrocannabinol (THC) plus prochlorperazine (PCZ) for refractory nausea and vomiting (N/V). *Proceedings of the American Society for Clinical Oncology* 1983;2:84.

4. Brock-Utne JG, Rubin J, Welman S, Dimopoulos GE, Moshal MG, Downing DW. The action of commonly used antiemetics on the lower oesophageal sphincter. *British Journal of Anaesthesia* 50(3);1978:295-298.

5. Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. *Annals of Internal Medicine* 1979;91(6):819-824.

6. Citron ML, Herman TS, Vreeland F, Krasnow SH, Fossieck (Fossieck Jr BE.). Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocanna-

binol for chemotherapy-induced nausea and vomiting. *Cancer Treatment Reports* 1985;69(1):109-112.

7. Colls BM, Ferry DG, Gray AJ, Harvey VJ, McQueen EG. The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. *New Zealand Medical Journal* 1980; 91(662):449-451.

8. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: An alternative antiemetic for cancer chemotherapy. *Archives of Disease in Childhood* 1986;61:502-505.

9. Ekert H, Waters KD, Jurk KH, Mobilia J, Loughnan P. Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. *Medical Journal of Australia* 1979;2(12):657-659.

10. Fan P. Cannabinoid agonists inhibit the activation of 5-HT_3 receptors in rat nodose ganglion neurons. *Journal of Neurophysiology* 1995;73(2):907-910.

11. Feigenbaum JJ, Richmond SA, Weissman Y, Mechoulam R. Inhibition of cisplatin-induced emesis in the pigeon by a nonpsychotropic synthetic cannabinoid. *European Journal of Pharmacology* 1989;169(1):159-165.

12. Fride E, Mechoulam R. Ontogenetic development of the response to anandamide and delta-9-tetrahydrocannabinol in mice. *Brain Research. Developmental Brain Research* 1996;95(1):131-134.

13. Frytak S, Moertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connnell MJ. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. *Annals of Internal Medicine* 1979;91(6):825-830.

14. Gralla RJ, Tyson LB, Bordin LA, Clark RA, Kelsen DP, Kris MG. Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treatment Report* 1984;68(1):163-172.

15. Hollister LE, Gillespie HK. Delta-8- and delta-9-tetrahydrocannabinol. Comparison in man by oral and intravenous administration. *Clinical Pharmacology and Therapeutics* 1973;14(3):353-357.

16. Kluin-Neleman JC, Neleman FA, Meuwissen OJ, and Maes RA. Δ^9-tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancer chemotherapy; a double-blind crossover trial against placebo. *Veterinary and Human Toxicology* 1979;21(5):338-340.

17. Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JL, Hamm J. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *Journal of Pain and Symptom Management* 1991;6(6):352-359.

18. Levitt M, Faiman C, Hawks R, Wilson A. Randomized double blind comparison of delta-9-tetrahydroicannabinol (THC) and marijuana as chemotherapy antiemetics. *Proceedings of the American Society for Clinical Oncology* 1984;3:91.

19. Levitt M, Wilson A, Bowman D, Faiman C, Kemel S, Krepart G. Dose vs response of tetrahydroannabinol (THC) vs prochlorperazine as chemotherapy antiemetics. *Proceedings of the American Society for Clinical Oncology* 1981;22:422.

20. McCabe M, Smith FP, Goldberg D, Macdonald J, Woolley PV, Warren R. Efficacy of tetrahydrocannabinol in patients refractory to standard anti-emetic therapy. *Investigational New Drugs* 1988;6(3):243-246.

21. Mitchelson F. Pharmacological agents affecting emesis. A Review (Part I). *Drugs* 1992;43(3):295-315.

22. Morrow GR, Hickok JT, Rosenthal SN. Progress in reducing nausea and emesis. Comparisons of ondansetron (Zofran), granisetron (Kytril) and tropisetron (Navoban). *Cancer* 1995;76:343-357.

23. Niiranen Aila, Mattson K. A crossover comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *American Journal of Clinical Oncology* 1985;8(4):336-340.

24. Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Archives of Internal Medicine* 1980;140(11):1431-433.

25. Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. *Cancer Chemotherapy and Pharmacology* 1986;17(3):285-288.

26. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *New England Journal of Medicine* 1980;302(3):135-138.

27. Sallan SE, Zinberg NE, Frei E. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *New England Journal of Medicine* 1975;293(16):795-797.

28. Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: A comparison of oral delta-9-THC and prochlorperazine. *Cancer* 1982;50(4):636-645.

29. Vinciguerra V, Moore T, Brennan E. Inhalation marijuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine* 1988;88(10):525-527.

30. Wamsley JK, Palacios JM. Histaminergic receptors. In Bjorklund A, Hokfelt T, Kuhar MJ (eds). *Handbook of chemical neuroanatomy*. Volume 3, *Classical transmitters and transmitter receptors in the CNS,* Part II, Amsterdam: Elsevier, 1984, pp. 386-406.

31. Wang SC. Emetic and antiemetic drugs. In Root WS, Hoffmann FG (eds.) *Physiological pharmacology II*. New York: Academic Press, 1965, pp. 255-328.

Chapter 15

Pain Therapy

Anita Holdcroft

Herbal preparations of cannabis have been used medically for thousands of years to treat pain. Chinese accounts report its use in painful rheumatic and female disorders. A mixture of hemp resin and wine was used to provide analgesia for surgery before general anesthetics were available.[7,17] In India its analgesic and antipyretic properties were recognized as well. Over the years its use has been recommended for a variety of inflammatory disorders, e.g., gout. In the mid-1800s Queen Victoria used it to treat painful menstrual cramps. In the same era it was Her Majesty's physician who wrote of its effectiveness in neuralgia, menstrual pains, migraine, and gout but not in sciatica.[22] The historical detailed descriptions of cannabis as a therapeutic agent document its use as an analgesic as one of its predominant features.

PAIN DISORDERS AND THEIR TREATMENTS

Pain is a symptom and is always subjective.[18] Acute traumatic pain is an unpleasant emotional and sensory experience. If it lasts beyond the time for tissue repair then it becomes chronic and may be neurogenic, inflammatory, or nociceptive in origin. Pain may be present continuously or intermittently. Therapies for pain relief are based on (1) pain severity, which has been described as mild, moderate, and severe, and with corresponding treatments for each type of severity, the so-called "WHO analgesic ladder";[1] (2) duration; and (3) underlying pathophysiology. For example, in terminal cancer pain, treatments which can have serious side effects are considered applicable. This has been the basis for the use of morphine in terminal cancer pain since addiction is not considered to be a significant problem in this case. Clinical trials of tetrahydrocannabinol (THC) have been conducted in terminal cancer pain so that long-term side effects could be avoided. In the

core curriculum for professional education in pain, cannabinoids are listed as adjuvants to routine analgesics.[5]

Drugs and their formulations have been designed to match the frequency of pain onset and recurrence. The inhalational route using nitrous oxide is recommended in situations in which there is an acute severe pain such as may be experienced by women during labor. When pain is long lasting, short-acting drugs may only be acceptable if they are formulated as slow release preparations to avoid multiple administrations. The inhalational administration of cannabis provides a fast onset of the therapeutic effect and has also been considered to be a useful method by which to titrate the effects of the inhaled substances. However, when pain is chronic and continuous, an analgesic compound with prolonged activity may be preferred, and the oral route of cannabinoid administration may be preferable.

Pain from damaged nerves that often may not respond well to opioids has been an identified target for clinical trials of cannabinoids[2] (see also Chapter 8). This neuropathic pain is often managed with multiple therapies and cannabinoids may be combined as adjuvants to reduce dosage and unwanted side effects of other drugs. Another identified clinical syndrome that is reported to respond to cannabinoids is migraine (see Chapter 16).

THEORETICAL AND EXPERIMENTAL DATA

Evidence for pain relief mediated by cannabinoid receptor agonists has been accumulating in animal experiments. The identification of two cloned cannabinoid receptors and their endogenous ligands have revived interest in the analgesic and anti-inflammatory properties of cannabinoids (see Chapters 7 and 8). Antinociceptive effects have been observed after acute noxious stimuli such as the tail flick[15] and hot-plate tests,[24] as well as after long-term inflammatory pains in both peripheral somatic[23] and visceral[12] structures.

The conduct of human experiments and clinical trials has been slower because of legal restrictions and the few cannabinoid compounds available for human use. Cannabis itself has been administered in cigarettes, and encapsulated in various forms of oil-based preparations for rectal or oral administration. THC (dronabinol) given in 10 to 25 mg doses did not change experimental pain thresholds[14] but it relieved cancer pain without significant mood effects.[3] A potent synthetic cannabinoid, levonantradol, was significantly more effective as a postoperative analgesic than placebo in a randomized double-blind placebo-controlled trial, although it caused more sedation and dizziness.[13]

The evidence for cannabinoids as analgesics has been studied in regular smokers of cannabis. The methodology was not reported to be randomized or double-blind. Twenty men smoked a single dose of 12 mg THC while six

men received placebo.[8,9] A significant decrease in pain thresholds and tolerance to electrical stimulation was recorded in the THC group. The limitations of this study are considerable. First, regular cannabis smokers were the chosen subjects. Cannabis has a long half-life and can accumulate in body tissues. Thus, tissue cannabinoid concentrations would have been variable. Second, there was no wash out time for residual cannabinoids nor any estimate of their concentration in tissues or urine obtained prior to the studies. Third, the placebo group was small and may have biased the results.

In a group of dental patients, a crossover study used the intravenous route for either placebo, diazepam (0.157mg/kg) or THC in doses of 0.022mg/kg and 0.044mg/kg prior to oral surgery.[21] Pain thresholds were measured at the glabellar eminence with a pressure algometer and from an electric signal delivered at the acromion process for up to 30 min after administration of the trial drug or placebo. During this time oral surgery was performed with the patient awake and receiving "partial" local anesthesia with adrenaline. The THC groups experienced a statistical increase in pain threshold to both experimental stimuli but no change in pain tolerance. The combination of partial pain control measures, experimental and clinical pain is a complicated situation from which it is difficult to draw firm conclusions on analgesic effects of THC.

CLINICAL TRIAL DATA AND CASE HISTORIES

Anecdotal accounts of the activity of cannabinoids include analgesia for acute and chronic pain, and painful muscle spasms which occur in multiple sclerosis and spinal cord injury. For example, an individual case study has been reported of a patient suffering from neurogenic pain who, following amputation, found that THC was more effective than conventional therapies in reducing phantom limb pain.[6] This follows the description by Dunn and Davis[4] of the use of THC for relieving phantom limb pain. Such case histories provide only limited evidence. Improved methodology with more objective criteria can be obtained by clinical studies in individual patients using a randomized double-blind placebo-controlled design. A patient with painful spasticity from spinal injuries was studied and the analgesic effects of oral doses of THC 5 mg, codeine 50 mg, and placebo were compared.[16] Both active preparations were significantly better than placebo and the only significant difference in the active drugs was that THC relieved spasticity better than codeine.

A cannabis extract was administered orally in a randomized placebo-controlled crossover study for six weeks (50 mg THC daily) in a patient with a ten year history of acute on chronic abdominal pain due to familial Mediterranean fever who required daily morphine, 30 mg, for analgesia.[10] The extract contained THC 5.75 percent, CBD 4.73 percent, and cannabinol

2.42 percent and was administered as 10 mg THC doses five times daily. CBD is known to antagonize the psychotropic effects of THC (see Chapter 33). Baseline and escape morphine usage was measured during the active and placebo weeks as well as visual analogue scores (VAS) for pain intensity. A highly significant morphine-sparing effect for both escape and total morphine consumption was observed during the weeks in which cannabis was regularly administered ($p < 0.001$).[11] Although cannabis is known to have antiemetic properties, its administration was accompanied by nausea which limited the acceptability of this preparation. This trial also raised other issues, such as withdrawal symptom management during the placebo phase of chronic cannabis use and the possibility of tolerance to the preparation used (see also Chapter 23).

In a randomized double-blind crossover placebo-controlled study of oral medication for pain in 10 terminal cancer patients Noyes and colleagues[19] compared 5, 10, 15, and 20 mg THC in single doses with placebo after the patient's regular medication had been withheld. A dose-related analgesic effect was observed with pain relief being significantly better than placebo at the two higher doses. Peak effects of 20 mg THC were noted five hours after dosing. A larger study of 36 terminally ill patients with cancer pain was then designed to compare 10 and 20 mg THC with 60 and 120 mg codeine and placebo.[20] In the study, 10 mg THC was slightly less effective than 60 mg codeine and 20 mg was slightly more effective than 120 mg codeine. The effect on pain relief was significantly superior to placebo at these higher doses. The higher dose of THC, however, was associated with an unacceptably high incidence of side effects such as sedation and incoordination.

SUMMARY

Cannabinoids have antinociceptive, anti-inflammatory, and antihyperalgesic activity mediated through central and peripheral mechanisms which are elucidated in Chapters 8 and 10. A small number of controlled clinical trials suggest that cannabis and THC have analgesic properties, but at a therapeutic dose limited by side effects that could restrict their use in ambulant patients. The plant material which contains CBD, an agent that antagonizes the psychotropic effects of THC, may have benefits by reducing these unwanted side effects. However, these side effects are probably no more severe than those of standard acute and chronic pain therapies and have not been as life threatening as those from morphine. The development of specific receptor ligands particularly for the peripheral receptors may influence the pharmacology of pain management in the future.

REFERENCES

1. *Cancer Pain Relief.* Geneva: World Health Organization, 1986, p. 51.

2. *Cannabis: The scientific and medical evidence.* Select Committee on Science and Technology. House of Lords, 9th Report session, 1997-98. London: The Stationery Office, 1998.

3. Davies BH, Weatherstone RM, Graham JDP, Griffiths RD. A pilot study of orally administered delta-1-(trans)-tetrahydrocannabinol in the management of patients undergoing radiotherapy for carcinoma of the bronchus. *British Journal of Pharmacology* 1974;1:301-306.

4. Dunn M, Davis R. The perceived effects of marijuana on spinal cord injured males. *Paraplegia* 1974;12(3):175.

5. Fields HL, ed. *Core curriculum for professional education.* International Association for the Study of Pain. Seattle, WA: IASP Press, 1991, p. 28.

6. Finnegan-Ling D, Musty RE. Marinol and phantom limb pain; a case study. In *1994 Symposium on the Cannabinoids.* Burlington, VT: International Cannabinoid Research Society, 1994, p. 53.

7. Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine.* New Haven, CT: Yale University Press, 1993.

8. Hill SY, Goodwin DW, Schwin R, Powell B. Marihuana: CNS depressant or excitant? *American Journal of Psychiatry* 1974;131(3):313-315.

9. Hill SY, Schwin R, Goodwin DW, Powell B. Marihuana and pain. *Journal of Pharmacology and Experimental Therapeutics* 1974;188(2):415-418.

10. Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 1997;52(5):483-488.

11. Holdcroft A, Smith M, Smith B, Hodgson H, Evans F. Clinical trial experience with cannabinoids. *Pharmaceutical Science* 1997;3:546-550.

12. Jaggar SI, Hasnie FS, Sellaturay S, Rice ASC. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB_2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998;76(1-2):189-199.

13. Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantrodol and placebo in acute postoperative pain. *Journal of Clinical Pharmacology* 1981;21(Suppl):320S-326S.

14. Karniol IG, Shirakawa I, Takahashi RN, Knobel E, Musty RE. Effects of delta-9 tetrahydrocannabinol and cannabinol in man. *Pharmacology* 1975;13(6): 502-512.

15. Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. *Journal of Pharmacology and Experimental Therapeutics* 1991;258(2):517-523.

16. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-THC shows antispastic and analgesic effects in a single case double blind trial. *European Archives of Psychiatry and Clinical Neuroscience* 1990;240(1):1-4.

17. Mechoulam R. The pharmacology of *Cannabis sativa*. In Mechoulam R, ed. *Cannabinoids as therapeutic agents*. Boca Raton, FL: CRC Press, 1986.

18. Mersky H, Bogduk N, eds. *Classification of Chronic Pain. Descriptions of chronic pain syndromes and definition of pain terms*. International Association for the Study of Pain. Seattle, WA: IASP Press, 1994.

19. Noyes R, Brunk SF, Baram DA, Canter A. Analgesic effects of delta-9-THC. *Journal of Clinical Pharmacology* 1975;15(2-3):139-143.

20. Noyes R, Brunk SF, Avery DH, Canter A. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics* 1975;18(1):84-89.

21. Raft D, Gregg J, Ghia J, Harris L. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain: Psychological correlates of the analgesic response. *Clinical Pharmacology and Therapeutics* 1977;21(1):26-33.

22. Reynolds JR. Therapeutic uses and toxic effects of *Cannabis indica*. *Lancet* 1890;1:637-638.

23. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB_1 receptors. *Pain* 1998;75(1): 111-119.

24. Welch SP, Stevens DL. Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine in mice. *Journal of Pharmacology and Experimental Therapeutics* 1992;262(1):10-18.

Chapter 16

Migraine

Ethan Russo

MIGRAINE AND ITS SYMPTOMS

Migraine is an ancient affliction, and one of humankind's most recalcitrant maladies. In essence, migraine is defined as a syndrome with headache, often hemicranial, which includes some combination of the following symptoms: a beating pain quality, "lightning pains," nausea, vomiting or anorexia, photophobia and phonophobia, visual disturbance such as hemianopsia, blurring, fortification spectra or other visual perturbations, and a strong genetic predilection. Migraine may include an aura (neurological prodromal disturbance) or lack this warning (simple migraine).

Migraine afflicts 14 percent of adult females and 8 percent of males.[19] Its cost to Western economies is staggering, between $5 billion and $17 billion annually in the United States alone. In total numbers, some 34.9 million people in that country suffer moderate to severe migraine with attendant disability.[39] Those who suffer from migraines perceive themselves as seriously afflicted by this disorder, inasmuch as their subjective burden produces results more severe than patients suffering depression, heart disease, osteoarthritis, and diabetes.[31,37] It is thus apparent that migraine is a serious disorder whose treatment must be equal to a difficult task.

STANDARD TREATMENT OF MIGRAINE

Drug treatment of migraine may either be symptomatic at the time of attack or prophylactic with daily medicine. Early intervention is problematical due to gastroparesis, and, thus, parenteral treatments are frequently necessary in severe attacks.

Symptomatic agents for migraine include simple analgesics (aspirin, ibuprofen, naproxen); opiates (codeine, meperidine); neuroleptics (chlorpro-

mazine, promethazine); ergots (ergotamine and dihydroergotamine); and the latest "gold standard," the triptans (sumatriptan and numerous others). About 70 percent of people respond to subcutaneous administration of sumatriptan.[23] However, many have significant complaints of side effects that limit usage.

Prophylactic drugs for migraine include beta-blockers (propranolol, atenolol); antidepressants (tricyclic or selective serotonin reuptake inhibitor); calcium entry blockers (verapamil, flunarizine), anti-inflammatory drugs (naproxen); and many others. In migraine, as with many chronic neurological disorders, some 70 percent of patients respond to simple approaches, while 20 percent are more recalcitrant, and 10 percent of cases defy multiple treatment efforts.

CLINICAL HISTORY OF CANNABIS IN MIGRAINE TREATMENT

Cannabis has been a recognized treatment for migraine in the Ayurvedic medicine of India since the sixth and seventh centuries, and perhaps for as long as 3,000 years.[5,9] An unequivocal account of parenteral application of cannabis (intranasal) was noted by Ibn Sahl, a Nestorean physician in Persia in the ninth century.[17] Culpeper commended hemp for inflammations of the head in the seventeenth century.[7]

From Clendinning's trials on migraine patients published in 1843,[6] to the observations of Fishbein (an American Medical Association president) in 1942,[13] there was a century of sanctioned Western medical usage of cannabis for the indication of headache, both symptomatically and prophylactically. Its enthusiastic adherents in the United States and in Europe included Russell Reynolds, Weir Mitchell, Ringer, Gowers, and Osler.[35] Cannabis was employed by extract or smoking to treat headache and was labeled an "outstanding agent."[8] Critics label this usage "anecdotal" despite the fact that patients were improved on cannabis treatment, worse without it, and improved again when it was resumed. These criteria resemble those of Koch's Postulates as suggested proof of efficacy.

In the end, cannabis was lost to Western medicine, not due to its pharmacological failure, but rather to poor quality control, and ultimately to politically motivated legislative fiat. It was nevertheless still employed as a homeopathic remedy for migraine in the former East Germany in the mid 1950s.[1]

Ethnobotanical treatment of headache with cannabis persists in India, Southeast Asia, China, and North Africa.[3,22,33]

Clinical data from the West on the efficacy of cannabis in migraine treatment is currently confined to case histories, due to a legislative prohibition on therapeutic trials in humans. This has occurred in spite of the recommendations of numerous government commissions, including that of President

Nixon in 1972, wherein migraine was specifically singled out as a disease worthy of research trials.[29]

In 1987, el-Mallakh studied three heavy cannabis smokers who reported migraines after cessation of its usage.[10] One returned to cannabis, with resumed symptomatic control.

Grinspoon and Bakalar included a section on cannabis in migraine treatment in their book.[14] One vignette described a woman's odyssey through various standard pharmaceuticals without relief, which was subsequently attained by cannabis smoking. Her two daughters also found benefit when so afflicted.

Similarly, Mikuriya has described numerous successes with cannabis and THC (dronabinol) treatment of migraine on the World Wide Web.[27,28]

Another published report[34] described successful symptomatic relief of migraine with cannabis smoking when ergotamine and other agents failed. The patient also noted a markedly decreased frequency of attacks.

THEORETICAL AND EXPERIMENTAL DATA WITH THC PERTINENT TO MIGRAINE

THC minimizes the release of serotonin from the platelets of migraine sufferers.[41]

Spadone provided evidence that THC stimulates the synthesis of serotonin and its brain content, favoring its synaptosomal release and inhibiting uptake.[38] These mechanisms may also help to explain migraine efficacy for this agent.

Anandamide, an endogenous cannabinoid, has a similar pharmacological profile to THC, including an inhibitory effect on cyclic AMP in target cells, which, though widespread in the brain, cluster in nociceptive areas[16] (see also Chapter 8). Burstein[4] has reviewed the relationship of cannabinoids and eicosanoids to inflammation, finding support for analgesic mechanisms. Additionally, THC and other components of cannabis may affect the "sterile inflammation" observed in migraine. For more detail, see Chapter 10.

Anandamide and other cannabinoid agonists (such as THC) inhibit rat serotonin type 3 (5-HT3) receptors.[11] The latter effect would support antiemetic properties of cannabis in migraine, and also a modulation of pain mechanisms (see Chapter 14).

Meng and colleagues have demonstrated that THC is involved in an analgesic brainstem circuit that interacts with opiate pathways.[26] In addition, THC experimentally increases beta-endorphin levels.[43] Depletion of endorphins has been measured in cerebrospinal fluid (CSF) during attacks[12] and is theoretically responsible for effects such as migraine hyperalgesia and photophobia. For more information on nociceptive effects and mecha-

nisms of cannabinoids and the endocannbinoid system,[18,42] see Chapters 8 and 15.

Boger and colleagues have demonstrated an 89 percent relative potentiation of the 5-HT_1A receptor response, and a 36 percent inhibition of the 5-HT_2A receptor response by anandamide.[2] A similar effect by THC is likely. These observations support efficacy for cannabinoids in acute symptomatic migraine treatment (agonistic activity at 5-HT_1A) and in prophylactic treatment of chronic headache (antagonistic activity at 5-HT_2A).[32]

Mailleux and Vanderhaeghen[21] have also shown that THC regulates substance P and enkephalin mRNA levels in the basal ganglia.

An important neurochemical link of the NMDA/glutamate system to trigeminovascular nociception in migraine has been reviewed in detail.[40] THC serves as a partial agonist that acts presynaptically to modulate glutamatergic transmission.[36] Hampson and colleagues have provided elegant demonstration of the ability of the THC and cannabidiol components of cannabis to act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA, and kainate receptors[15] (see also Chapter 9).

Italian researchers Nicolodi and Sicuteri have elucidated the role of NMDA antagonists in eliminating hyperalgesia in migraine, and possible other conditions.[30] Given the previously described observations and relationships, it is logical that prolonged use of THC prophylactically may exert similar benefits, as was espoused in cures of chronic daily headache claimed in the nineteenth century with regular use of extract of Indian hemp.[20]

Endogenous cannabinoids and their inactive metabolites combine to boost physiological responses (the "entourage effect").[25] Given the likely contributions of cannabis flavonoids and essential oils to therapeutic effects on mood, inflammation, and pain reviewed by McPartland and Pruitt[24] and in this volume, one can easily see support for Mechoulam's quotation: "This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them."[25]

VALUE AND PLACE OF CANNABIS IN MIGRAINE TREATMENT

The information reviewed indicates that cannabis has a long-established history of efficacy in migraine treatment, with current supportive biochemical and pharmacological evidence. Its unique ability to modulate various serotonergic receptor subtypes, inhibit glutamatergic-mediated toxicities, simultaneously provide anti-inflammatory activity and provide acute symptomatic and chronic preventive relief make cannabis unique among available treatments for this disorder.

This author's personal experience in talking to several hundred migraine sufferers who have employed cannabis is that 80 percent have noted improvement, often with complete symptomatic relief. That this has occurred without any quality control of the herb whatsoever is very significant. Many report the ability to titrate their dosage through smoking so that they achieve relief without cognitive or motor impairment. The latter is not the case with oral THC (dronabinol or Marinol), whose slow and variable gastrointestinal absorption have made it a poorer choice in acute cases.

REFERENCES

1. Auster F, Schäfer J. *Arzneipflanzen*. Leipzig: Veb Georg Thieme, 1955.

2. Boger DL, Patterson JE, Jin Q. Structural requirements for 5-HT2A and 5-HT1A serotonin receptor potentiation by the biologically active lipid oleamide. *Proceedings of the National Academy of Sciences of the United States of America* 1998,95(8):4102-4107.

3. Boulos L. *Medicinal plants of North Africa, Medicinal plants of the world.* No. 3. Algonac, MI: Reference Publications Inc, 1983.

4. Burstein S. Eicosanoids as mediators of cannabinoid action. In Murphy L, Bartke A, eds. *Marijuana/Cannabinoids: Neurobiology and neurophysiology of drug abuse*. Boca Raton, FL: CRC Press, 1992.

5. Chopra IC, Chopra RW. The use of cannabis drugs in India. *Bulletin on Narcotics* 1957;9:4-29.

6. Clendinning J. Observation on the medicinal properties of *Cannabis sativa* of India. *Medico-Chirurgical Transactions* 1843;26:188-210.

7. Culpeper N. *Culpeper's complete herbal: Consisting of a comprehensive description of nearly all herbs with their medicinal properties and directions for compounding the medicines extracted from them.* London; New York: W. Foulsham, 1994.

8. Dinand AP. *Handbuch der Heilpflanzenkunde.* Esslingen, München: I.F. Schreiber, 1921.

9. Dwarakanath C. Use of opium and cannabis in the traditional systems of medicine in India. *Bulletin on Narcotics* 1965;17:15-19.

10. el-Mallakh RS. Marijuana and migraine. *Headache* 1987;27(8):442-443.

11. Fan P. Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion. *Journal of Neurophysiology* 1995;73(2):907-910.

12. Fettes I, Gawel M, Kuzniak S, Edmeads J. Endorphin levels in headache syndromes. *Headache* 1985;25(1):37-39.

13. Fishbein M. Migraine associated with menstruation. *Journal of the American Medical Association* 1942;237:326.

14. Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine*. Revised and expanded edition. New Haven, CT: Yale University Press, 1997.

15. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Δ^9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95(14):8268-8273.

16. Herkenham MA. Localization of cannabinoid receptors in brain: Relationship to motor and reward systems. In Korman SG, Barchas JD, eds. *Biological Basis of Substance Abuse*. London: Oxford University, 1993.

17. Kahl O. Sabur ibn Sahl *Dispensatorium Parvum (al-Azrabadhin al-Saghir)*. Leiden: E.J. Brill. 1994.

18. Lichtman AH, Cook SA, Martin BA. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: Evidence supporting periaqueductal gray involvement. *Journal of Pharmacology and Experimental Therapeutics* 1996;276(2):585-593.

19. Linet MS, Stewart WF, Celentano DD, Ziegler D, Sprecher M. An epidemiologic study of headache among adolescents and young adults. *Journal of the American Medical Association* 1989;261(15):2211-2216.

20. Mackenzie S. Remarks on the value of Indian hemp in the treatment of a certain type of headache. *British Medical Journal* 1887;1:97-98.

21. Mailleux P, Vanderhaeghen JJ. Delta-9-tetrahydrocannabinol regulates substance P and enkephalin mRNAs levels in the caudate-putamen. *European Journal of Pharmacology* 1994;267(1):R1-3.

22. Martin MA. Ethnobotanical aspects of cannabis in Southeast Asia. In Rubin V, ed. *Cannabis and culture*. The Hague; Paris: Mouton Publishers, 1975.

23. Mathew NT. Serotonin 1D (5-HT1D) agonists and other agents in acute migraine. *Neurologic Clinics* 1997;15(1):61-83.

24. McPartland JM, Pruitt PL. Side effects of pharmaceuticals not elicited by comparable herbal medicines: The case of tetrahydrocannabinol and marijuana. *Alternative Therapies in Health and Medicine* 1999;5 (4):57-62.

25. Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: The ongoing story of cannabis. *Natural Product Reports* 1999;16 (2):131-143, p. 196.

26. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. *Nature* 1998;395 (6700):381-383.

27. Mikuriya TH. Medicinal uses of cannabis at a Buyers' Club, 1995. Available from <http://www.druglibrary.org/schaffer/hemp/migrn2.htm>.

28. Mikuriya TH. Chronic migraine headache: Five cases successfully treated with Marinol and/or illicit cannabis, 1997. Available from <http://www.druglibrary.org/schaffer/hemp/migrn1.htm>.

29. National Commission on Marihuana and Drug Abuse. *Marihuana: A signal of misunderstanding*. Washington, DC: New American Library, 1972.

30. Nicolodi M, Sicuteri F. Negative modultors [sic] of excitatory amino acids in episodic and chronic migraine: Preventing and reverting chronic migraine. Special lecture 7th INWIN Congress. *International Journal of Clinical Pharmacology Research* 1998;18 (2):93-100.

31. Osterhaus JT, Townsend RJ, Gandek B, Ware Jr JE. Measuring the functional status and well-being of patients with migraine headache. *Headache* 1994;34 (6):337-343.

32. Peroutka SJ. Developments in 5-hydroxytryptamine receptor pharmacology in migraine. *Neurologic Clinics* 1990;8 (4):829-839.

33. Perry LM, Metzger J. *Medicinal plants of East and Southeast Asia: Attributed properties and uses*. Cambridge: MIT Press, 1980.

34. Petro D. Spasticity and chronic pain. In Mathre ML, ed. *Cannabis in medical practice*. Jefferson, NC: McFarland, 1997.

35. Russo EB. Hemp for headache: An in-depth historical and scientific review. *Journal of Cannabis Therapeutics*, 2001;1(2):21-92.

36. Shen M, Thayer SA. Δ^9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. *Molecular Pharmacology* 1999;55 (1):8-13.

37. Solomon GD, Skobieranda FG, Gragg LA. Quality of life and well-being of headache patients: Measurement by the medical outcomes study instrument. *Headache* 1993;33 (7):351-358.

38. Spadone C. Neurophysiologie du cannabis. *Encephale* 1991;17 (1):17-22.

39. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *Journal of the American Medical Association* 1992;267 (1):64-69.

40. Storer RJ, Goadsby PJ. Trigeminovascular nociceptive transmission involves *N*-methyl D-aspartate and non-*N*-methyl D-aspartate glutamate receptors. *Neuroscience* 1999;90 (4):1371-1376.

41. Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. *International Journal of Clinical Pharmacology Research* 1985;5 (4):243-246.

42. Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by the release of the endogenous cannabinoid anandamide. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96 (21):12198-12203.

43. Wiegant VM, Sweep CG, Nir I. Effect of acute administration of delta 1-tetrahydrocannabinol on beta-endorphin levels in plasma and brain tissue of the rat. *Experientia* 1987;43 (4):413-415.

Chapter 17

Spastic Disorders

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INTRODUCTION

Several U.S. states have "legalized" marijuana for medical use in the past years. For many reasons, including that marijuana is still illegal in U.S. federal law, and due to demand from patients who claim successful relief from marijuana use, these voter-initiated bills resulted in unprecedented legal, political, and scientific repercussions. Several notable scientific meetings were held in 1997-1998 in Europe and the United States to examine the issue of medical marijuana, and reviews on the medical benefits of cannabis have been published.[5,21]

Marijuana continues to be used illegally for self-medication for spasticity associated with multiple sclerosis (MS) and spinal cord injury (SCI), the extent of use by patients is unknown. Dronabinol (Marinol; Δ^9-THC) and nabilone (Cesamet) have been used occasionally in clinical trials for treatment of spasticity. In the preclinical area, discoveries of brain cannabinoid receptors and their endogenous ligands (see Chapter 7) and other cannabinoid mechanisms have accelerated research with the hypothesis that cannabinoids might be developed as therapeutic agents.

SPASTICITY AND SPASTIC DISORDERS

Spasticity is a specific type of muscle hypertonia that develops after supraspinal or spinal lesions occur in descending corticospinal (pyramidal) or other motor pathways.[1,15] In the spinal cord, when spasticity occurs, there

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is increased activity of alpha motoneurons and excitatory interneurons, and decreased activity of inhibitory interneurons.[32] This results in facilitation of excitatory glutamate neurons, and inhibition of inhibitory GABA neurons.[15,32] A separate ceruleus-spinal projection also modulates the activity of spinal motoneurons via a noradrenergic mechanism.[15] Spasticity, along with flexor and extensor spasms, clonus, cerebellar limb and gait ataxia, intention tremor, and acute, chronic, and paroxysmal pains are often features of multiple sclerosis (MS) and/or spinal cord disease or injury.[1] Baclofen, a $GABA_B$ receptor agonist, and tizanidine, an $alpha_2$ receptor agonist, are commonly used spasmolytic drugs. There are no good treatments for ataxia, intention tremor, and chronic pain.[1] Antiepileptic drugs, especially carbamazepine or baclofen, or surgery are the most common treatments of the paroxysmal pains such as trigeminal neuralgia.[1]

MARIJUANA AND CANNABINOIDS IN SPASTIC DISORDERS

Reviews and critiques of the clinical literature on spasticity effects have been published.[7,8,34] The bulk of the marijuana reports are anecdotal, and all of the clinical trials used small numbers of patients and often lack controls. Although no single study would be considered conclusive, taken together, reports suggest that marijuana, Δ^9-THC, and nabilone likely have beneficial symptomatic activity in conditions with spasticity. Few reports cite any side effects. Anecdotal reports of decreases in spasticity, tremor, and pain have been reported in many patients.[7,8,18,36,37] Scott Imler, who managed one of the cannabis buyers' clubs in California, illustrates:

> I have a videotape of a quadriplegic whose legs are bucking and bouncing. A couple of puffs and the spasms stop cold. . . . Our quad members tell us this happens every morning: They wake up with knees in their mouths, stiff as a board, and two or three puffs later, their muscles relax . . . (Medical Use of Marijuana, HMS Beagle Debate, <http://www.biomednet.com/hmsbeagle/30/cutedge/overview. htm>)

Patients who have completed anonymous surveys regarding use of marijuana for symptoms of multiple sclerosis and spasticity report decreases in spasms, tremor, and pain: 10 SCI patients,[14] 43 SCI patients,[25] 112 MS patients,[9] 106 SCI patients.[10] In a survey of 128 German users of medical marijuana, 10.8 percent used it for symptoms of multiple sclerosis, 3.6 percent for spasticity, and 2.4 percent for symptoms associated with spinal cord injury.[43] Furthermore, there have been two small studies of MS patients who smoked marijuana, the first being an open-label study (n = 1). The patient showed decreased spasticity, tremor, and ataxias.[29] The second, a double-blind study with placebo control (n = 10), measured only balance and not

spasticity or other signs.[17] These authors found that smoked marijuana adversely affected balance in the marijuana group when assessed by sophisticated electronic equipment and videotaping, but not when assessed by the standard neurological exam. This is not surprising, since sensitive equipment rather than routine clinical exams are often required to detect neurological deficits in normal subjects given marijuana or Δ^9-THC.[7]

Δ^9-THC AND NABILONE

In a double-blind, placebo-controlled study, using oral Δ^9-THC (n = 9), spasticity in MS patients decreased when compared with placebo.[35] Using subjective reports in a double-blind, placebo-controlled crossover (n = 13), MS patients reported decreased spasticity.[49] Finally in a single-blind, placebo-controlled study, decreased tremor occurred in 2/8 MS patients.[6] Two studies have been conducted with spinal cord injured patients using Δ^9-THC. The first[19] was a double-blind placebo-controlled crossover (n = 5). Decreased spasticity was observed in 2/5 patients. In the second study,[28] a double-blind, placebo-controlled (n = 1), spasticity and pain were decreased. In a double-blind, placebo-controlled study using nabilone,[27] spasticity was also decreased. Oral and rectal preparations of Δ^9-THC administered to one MS patient and one SCI patient led to decreased spasticity and rigidity.[4]

A few of the studies[4,19,49] reported that Δ^9-THC produced adverse effects. This is not unexpected since these effects (dizziness, mental clouding, dry mouth, weakness) are typical subjective side effects of the drug. Anecdotal reports indicate that, when subjects have had experience with both drugs, smoked marijuana usually is preferred over oral Δ^9-THC.[10,18,37]

Symptomatic improvement of spasticity, intention tremor, ataxia, trigeminal neuralgia, and chronic pain would be uniquely important attributes of marijuana and cannabinoids. A controlled comparative study of marijuana, oral Δ^9-THC, and (smoked and oral) placebos, given repeatedly over time in a sufficient number of patients with spasticity, tremor, ataxia, and pain would do much to promote closure of argumentative debate about efficacy and safety of these drugs.

PRECLINICAL EFFECTS OF CANNABINOIDS

A Δ^9-THC analogue, and Δ^9-THC and cannabis extract, were shown to depress the polysynaptic linguomandibular reflex in the cat[3] and dog,[41] respectively. This effect is mediated at some supraspinal level and is consistent with spasmolytic activity.[3] However, in the spinal cord, Δ^9-THC was found to increase excitatory postsynaptic potentials (EPSP) and decrease inhibitory postsynaptic potentials (IPSP) at cat spinal motoneurons.[46] These

effects might tend to oppose spasmolytic activity. Interestingly, cannabidiol (CBD), a main nonpsychoactive constituent of cannabis, was found to produce the opposite effects of decreasing EPSP and increasing IPSP at cat spinal motoneurons.[47]

Recently, other findings indicate that CB_1 receptor agonists can have a major influence on the activity of the substantia nigra pars reticulata (SNr). Specifically, WIN 55,212-2[30,45] and CP 55,940[45] increased the firing rate of neurons in the SNr, and WIN 55,212-2[30] antagonized the inhibition of firing in the SNr by electrical stimulation of the striatum. Furthermore, WIN 55,212-2 blocked the increase in the firing rate of SNr neurons induced by chemical stimulation of the subthalamic nucleus.[42] The SNr is a major output nucleus of the basal ganglia[15] and is the site of the greatest abundance of CB_1 receptors in the brain.[16] In genetically spastic rats, the SNr was identified as a major supraspinal site of action for the muscle relaxing effects of two clinically used spasmolytic drugs, baclofen and tizanidine.[48] This appears to be a promising lead for future study with CB_1 receptor agonists.

Many reports indicate that CB_1 receptor agonists enhance GABA function in the brain.[26,34] Moreover, behavioral motor inhibition produced by Δ^9-THC or anandamide may be mediated through $GABA_B$ receptor activation.[40] It is generally accepted that CB_1 receptor agonists reduce transmitter release, via decreasing calcium-channel conductance, and decrease action potential generation, via increasing potassium-channel conductance.[33] Also, CB_1 receptor agonists have been found to inhibit presynaptic glutamic acid release in rat hippocampal cultures[44] (see also Chapter 9). If these cannabinoid effects act in tandem, and in the appropriate sites in brain and cord, then they would be analogous to the purported spasmolytic mechanism of action of baclofen.[32] That is, activation of postsynaptic $GABA_B$ receptors by baclofen increases potassium conductance, neuronal hyperpolarization, and subsequent presynaptic inhibition. Activation of presynaptic $GABA_B$ receptors by baclofen decrease calcium-channel conductance which in turn inhibits the release of glutamic acid.

Effects of CB_1 receptor agonists also may resemble those of tizanidine. One study has reported that an $alpha_2$ noradrenergic antagonist (yohimbine) given intrathecally at the lumbar spinal level blocked the antinociceptive response (mouse tail flick) of Δ^9-THC given intravenously.[22] The authors concluded that cannabinoids activate descending noradrenergic neurons resulting in antinociception via the stimulation of $alpha_2$ adrenergic receptors. Tizanidine stimulates $alpha_2$ adrenergic receptors which results in both a direct impairment of glutamate release from spinal interneurons, and a concomitant inhibition of the excitatory ceruleus-spinal pathway.[13,32] The connection between the spasmolytic and analgesic activities is that tizanidine also has antinociceptive activity, and this effect, like its spasmolytic activity,

is due to an alpha$_2$ adrenergic receptor-mediated inhibition of spinal interneuronal activity.[13]

As an important extension of the analgesic and glutamate effects discussed, recent evidence in mice indicates that there is a tonic modulation of nociceptive thresholds by spinal cannabinoid systems.[38] Further, these spinal cannabinoid systems made hypoactive by injection of antisense to the CB_1 receptor mRNA resulted in an NMDA-dependent hyperalgesia.[38] A similar hyperalgesia was found after injection of SR 141716A,[38] the latter a selective CB_1 receptor antagonist and inverse CB_1 agonist.[33] Presumably the hyperalgesia was due to release of glutamate which subsequently activated the NMDA receptor.[38] Hyperalgesia and allodynia (pain elicited by normally nonpainful stimuli) are characteristic features of the chronic and paroxysmal pains of MS and also of the chronic neuropathic pains of other conditions.[1] In one rat model of neuropathic pain (chronic sciatic nerve constriction injury), hyperalgesia and allodynia were greatly reduced by WIN 55,212-2.[20] These effects appear to be mediated by CB_1 receptors since the inactive enantiomer of WIN 55,212-2 was inactive in this model.[20] Curiously, in the only other reported model of neuropathic pain, HU-211 was shown to significantly reduce a rat behavior of self-mutilation following neuronal denervation.[51] HU-211, a cannabinoid which does not act on CB_1 or CB_2 receptors,[31] presumably produced this effect by a stereospecific, noncompetitive blockade of the NMDA receptor.[31]

The two other major features of MS which are potential targets for therapy by cannabinoids are intention tremor and ataxia. Yet, paradoxically, marijuana and Δ^9-THC appear to ameliorate these signs of MS, and yet they tend to cause these signs in laboratory animals and humans in some studies.[7] Although the clinical descriptions of cerebellar ataxia and intention tremor caused by MS[1] and the ataxia and tremor caused by marijuana or Δ^9-THC[7] appear to differ significantly, there are no human data to directly resolve this important paradox.

Interestingly, however, WIN 55,212-2 relieves symptoms of dystonia in mutant dystonic hamsters.[39] Cannabidiol attenuates dystonia and torticollis in mutant rats,[11] and apomorphine induced turning in rats with unilateral nigrostriatal lesions.[12] WIN 55,212-2 is considered to be a full CB_1 receptor agonist, while CBD may be a weak neutral or partial CB_1 receptor antagonist.[6,8] These differences in the data might suggest biphasic effects of CB_1 agonists and unidirectional effects of CB_1 antagonists. Further research is needed to test this hypothesis.

Delta-9-THC (or Δ^8-THC) was found to inhibit the development of the histological and clinical paralytic features of experimental autoimmune encephalomyelitis (EAE) and experimental autoimmune neuritis (EAN) in experimental animals.[23,24,50] EAE is the commonly used animal model for MS, while EAN is a commonly used animal model for Guillain-Barré syn-

drome.[24] Both of these disorders have in common a possible immunological etiology, and a focal demyelinating pathology.[1] Current drug treatments to reduce acute exacerbations or to prevent worsening of these diseases consist of various immunosuppressant therapies.[1] Δ^9-THC has immunosuppressant effects, presumably by acting on primarily CB_2 receptors located in the immune system.[33] These findings suggest that cannabinoid receptor agonists might affect the underlying disease process of MS.

Last, recent findings[2] have clearly established that cannabinoid CB_1 agonists can specifically ameliorate the signs of spasticity and tremor in an MS model in Biozzi ABH mice. Using this mouse model of chronic relapsing EAE, the CB_1 receptor agonists, WIN 55,212, Δ^9-THC, and methanandamide, as well as the selective CB_2 receptor agonist JWH-133, each blocked spasticity and tremor in the mutant mice. Further, the selective CB_1 receptor antagonist SR141716A and the selective CB_2 receptor antagonist SR144528 each reversed the effect of the CB_1 agonists; and when given alone, these cannabinoid antagonist drugs caused an exacerbation of these two clinical signs. In addition, treatment with palmitylethanolamide reduced spasticity in these mice.[2] This compound has agonist activity for CB_2-like receptors, but has no actions on the CB_1 receptor.[2,33] Taken together, it is possible that CB_2 receptor agonists may have therapeutic potential for treating MS symptoms without intoxicating effects. These results provide direct evidence that (1) cannabinoid agonists, particularly those acting at the CB_1 receptor, can ameliorate two major clinical signs of MS; (2) endogenously present anandamide or other endocannabinoids may be tonically active in the control of spasticity and tremor of MS; and (3) by implication of the results with Δ^9-THC, patient claims of reduction of spasticity and tremor from marijuana smoking are genuine pharmacological effects.

REFERENCES

1. Adams RD, Victor M, Ropper AH. eds. *Principles of neurology,* Sixth edition. McGraw-Hill, New York, 1997.

2. Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffmann JW, Layward L. Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 2000;404(6773):84-87.

3. Boyd ES, Meritt DA. Effects of a tetrahydrocannabinol derivative on some motor systems in the cat. *Archives Internationales de Pharmacodynamie et de Therapie* 1965;153:1-12.

4. Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y. The effect of orally and rectally administered delta-9-tetrahydrocannabinol on spasticity: A pilot study with 2 patients. *International Journal of Clinical Pharmacology and Therapeutics* 1996;34(10):446-452.

5. British Medical Association, David R Morgan, eds. *Therapeutic uses of cannabis*. Harwood Academic Publishers, London, 1998.

6. Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology* 1983;13(6):669-671.

7. Consroe P, Snider SR. Therapeutic potential of cannabinoids in neurological disorders. In Mechoulam R, ed. *Cannabinoids as therapeutic agents*. Boca Raton, FL: CRC Press Inc, 1986, pp. 21-49.

8. Consroe P, Sandyk R. Potential role of cannabinoids for therapy of neurological disorders. In Bartke A, Murphy L, eds. *Marijuana/cannabinoids: Neurobiology and neurophysiology*. Boca Raton, FL: CRC Press Inc, 1992, pp. 459-524.

9. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 1997;38(1):44-48.

10. Consroe P, Tillery W, Rein J, Musty RE. Reported marijuana effects in patients with spinal cord injury. *1998 Symposium on the Cannabinoids*. Burlington,VT: International Cannabinoid Research Society, 1998, p. 64.

11. Consroe P, Musty RE, Conti LH. Effects of cannabidiol in animal models of neurologic dysfunction. In Chesher G, Consroe P, Musty RE, eds. *Marihuana: An international research report*. Canberra: Australian Government Publishing Service, 1988;141-146.

12. Conti LH, Johanessen J, Musty RE, Consroe P. Anti-dyskinetic effects of cannabidiol. In Chesher G, Consroe P, Musty RE, eds. *Marihuana: An international research report*. Canberra: Australian Government Publishing Service, 1988, pp. 153-156.

13. Coward DM. Tizanidine: Neuropharmacology and mechanism of action. *Neurology* 1994;44(Suppl 9):6S-11S.

14. Dunn M, Davis R. The perceived effects of marijuana on spinal cord injured males. *Paraplegia* 1974;12(3):175.

15. Gilman S, Newman SW, eds. *Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology,* Ninth Edition. Philadelphia: F.A. Davis Company, 1996.

16. Glass M, Dragunow M, Faull RLM. Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* 1997;77(2):299-318.

17. Greenberg HS, Werness SAS, Pugh JE, Andrus RO, Anderson DJ, Domino EF. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clinical Pharmacology and Therapeutics* 1994;55(3):324-328.

18. Grinspoon L, Bakalar JB, eds. *Marihuana: The forbidden medicine*. New Haven, CT: Yale University Press, 1993.

19. Hanigan WC, Destree R, Truong XT. The effect of Δ^9-THC on human spasticity. *Clinical Pharmacology and Therapeutics* 1986;39:198.

20. Herzberg U, Eliav E, Bennett GJ, Kopin IJ. The analgesic effects of R(+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neuroscience Letters* 1997;221(2-3):157-160.

21. Joy JE, Watson SJ, Benson JA, eds. *Marijuana and medicine: Assessing the science base*. Washington, DC: Institute of Medicine, National Academy Press, 1999.

22. Lichtman AH, Martin BR. Cannabinoid-induced antinociception is mediated by a spinal alpha-2-noradrenergic mechanism. *Brain Research* 1991;559(2):309-314.

23. Lyman WD, Sonett JR, Brosnan CF, Elkin R, Bornstein MB. Δ^9-Tetrahydrocannabinol: A novel treatment of experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 1989;23(1):73-81.

24. Lyman WD. Drugs of abuse and experimental autoimmune diseases. In Friedman H, Specter S, Klein TW, eds. *Drugs of abuse, immunity and immunodeficiency*. New York: Plenum Press, 1991, pp. 81-92.

25. Malec J, Harvey RF, Cayner JJ. Cannabis effect on spasticity in spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 1982;63(3):116-118.

26. Maneuf YP, Crossman AR, Brotchie JM. Modulation of GABAergic transmission in globus pallidus by the synthetic cannabinoid WIN 55,212-2. *Synapse* 1996;22(4):382-385.

27. Martyn CN, Illis LS, Thom J. Nabilone in the treatment of multiple sclerosis. *Lancet* 1995;345(8949):579.

28. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *European Archives of Psychiatry and Clinical Neuroscience* 1990;240(1):1-4.

29. Meinck HM, Schönle PWA, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology* 1989;236(2):120-122.

30. Miller AS, Walker JM. Effects of a cannabinoid on spontaneous and evoked neuronal activity in the substantia nigra pars reticulata. *European Journal of Pharmacology* 1995;279(2-3):179-185.

31. Nadler V, Mechoulam R, Sokolovsky M. Blockade of $45Ca^2+$ influx through *N*-methyl-*D*-aspartate receptor ion channel by the non-psychoactive cannabinoid HU-211. *Brain Research* 1993;622(1-2):79-85.

32. Noth J. Trends in the pathophysiology and pharmacotherapy of spasticity. *Journal of Neurology* 1991;238:131-139.

33. Pertwee RG. Pharmacology of cannabinoid CB_1 and CB_2 receptors. *Pharmacology and Therapeutics* 1997;74(2):129-180.

34. Pertwee RG. The central neuropharmacology of psychotropic cannabinoids. *Pharmacology and Therapeutics* 1987;36(2-3):189-261.

35. Petro DJ, Ellenberger C. Treatment of human spasticity with Δ^9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 1981;21(8-9 supplement):413-416.

36. Petro DJ. Marihuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics* 1980;21(1):81-85.

37. Randall RC, ed. *muscle spasm, pain and marijuana therapy*. Washington, DC: Galen Press, 1991.

38. Richardson JD, Aanonsen L, Hargreaves KM. Hypoactivity of the spinal cannabinoid system results in NMDA-dependent hyperalgesia. *Journal of Neuroscience* 1998;18(1):451-457.

39. Richter A, Loscher W. (+)-WIN 55,212-2, a novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters. *European Journal of Pharmacology* 1994;264(3):371-377

40. Romero J, Garcia-Palomero E, Fernandez-Ruiz JJ, Ramos JA. Involvement of $GABA_B$ receptors in the motor inhibition produced by agonists of brain cannabinoid receptors. *Behavioural Pharmacology* 1996;7(3):299-302.

41. Sampaio CA, Lapa AJ, Valle JR. Influence of cannabis, tetrahydrocannabinol and pyrahexyl on the linguomandibular reflex of the dog. *Journal of Pharmacy and Pharmacology* 1967;19(8):552-554.

42. Sanudo-Pena MC, Walker JM. Role of the subthalamic nucleus in cannabinoid actions in the substantia nigra of the rat. *Journal of Neurophysiology* 1997;77(3):1635-1638.

43. Schnelle M, Grotenhermen F, Reif M, Gorter RW. Ergebnisse einer standardisierten Umfrage zur medizinischen Verwendung von Cannabisprodukten im deutschen Sprachraum, [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. *Forschende Komplementärmedizin [Research in Complementary Medicine]* 1999;6(Suppl 3) 28-36.

44. Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *Journal of Neuroscience* 1996;16(14):4322-4334.

45. Tersigni TJ, Rosenberg HC. Local pressure application of cannabinoid agonists increases spontaneous activity of rat substantia nigra pars reticulata neurons without affecting response to iontophoretically-applied GABA. *Brain Research* 1996;733(2):184-192.

46. Turkanis SA, Karler R. Effects of delta-9-tetrahydrocannabinol on cat spinal motoneurons. *Brain Research* 1983;288(1-2):283-287.

47. Turkanis SA, Karler R. Cannabidiol-caused depression of spinal motoneuron responses in cats. *Pharmacology, Biochemistry and Behavior* 1986;25(1):89-94.

48. Turski L, Klockgether T, Schwarz M, Turski WA, Sontag KH. Substantia nigra: A site of action of muscle relaxant drugs. *Annals of Neurology* 1990;28:341-348.

49. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Δ^9-THC in the treatment of spasticity associated with multiple sclerosis. *Advances in Alcohol and Substance Abuse* 1987;7(1):39-50.

50. Wirguin I, Mechoulam R, Breuer A, Schezen E, Weidenfeld J, Brenner T. Suppression of experimental autoimmune encephalomyelitis by cannabinoids. *Immunopharmacology* 1994;28(3):209-214.

51. Zeltser R, Seltzer Z, Eisen A, Feigenbaum JJ, Mechoulam R. Suppression of neuropathic pain behavior in rats by a nonpsychotropic synthetic cannabinoid with NMDA receptor-blocking properties. *Pain* 1991;47(1):95-103.

Chapter 18

Movement Disorders

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Patients suffering from neurologic movement disorders either move too much (hyperkinetic disorders) or too little (hypokinetic disorders). Hyperkinetic disorders are characterized by involuntary movements such as tics, tremor, dystonia, myoclonus, and chorea. Hypokinetic (bradykinetic) disorders clinically result in parkinsonian features. The underlying cause of the majority of movement disorders is accepted as a dysfunction of basal ganglia-thalamo-cortical circuits.

Since central cannabinoid CB_1 receptors have been found to be located at high concentrations in the output nuclei of the basal ganglia (on the axon terminals of striatal efferent neurons projecting to the globus pallidus and substantia nigra pars reticulata [SNr]), it has been suggested that cannabinoids regulate motor activity.[13] Several studies provided evidence that a general role of the endogenous cannabinoid transmission is the manipulation of other transmitter systems.[27] The three main transmitters present in the basal ganglia are glutamate (predominantly excitatory transmitter), γ-aminobutyric acid (GABA, predominantly inhibitory transmitter), and dopamine. Cannabinoids have been found to reduce GABA reuptake in the globus pallidus lateralis (GPl),[15] regulate the activity of SNr neurons by inhibition of GABA inputs,[17] and inhibit the release of glutamate from the subthalamic nucleus in the SNr.[31] Furthermore, cannabinoid receptors are co-localized both with dopamine D_1 receptors on striatonigral dynorphin/substance P-containing neurons and with dopamine D_2 receptors on striatopallidal enkephalinergic neurons, suggesting that cannabinoids influence dopaminergic processes.[13] In addition, evidence suggests that CB_1 receptors themselves are

tonically active and therefore participate in the regulation of motor activity.[1,11]

Several animal studies support the hypothesis that cannabinoids regulate motor activity: cannabinoids potentiate neuroleptic-induced hypokinesia,[18] and induce catalepsy[24] and turning behavior.[35] Anandamide, an endogenous ligand of the cannabinoid receptor, has been found to reduce locomotor activity.[8]

A small number of clinical case reports and controlled studies in volunteers suggest that cannabinoids might be useful in the therapy of movement disorders. Based on experimental data and animal studies, therapeutic strategies using cannabinoids have so far predominantly focused on hyperkinetic movement disorders.

GILLES DE LA TOURETTE SYNDROME

Gilles de la Tourette Syndrome (Tourette's syndrome, TS) is a complex neuropsychiatric disorder of unknown etiology characterized by waxing and waning motor and one or more vocal tics, present throughout a period of more than a year, with onset before age 18. In many patients a variety of behavioral disorders is associated. Basal ganglia circuits projecting to the frontal cortex and limbic regions are thought to be pathophysiologically involved. Furthermore, evidence suggests that the dopaminergic system plays a role in TS pathology.

To date, therapy of TS is difficult, and in many patients, remains unsatisfactory. Dopamine receptor blockers (neuroleptics) are the treatment of choice for the suppression of tics. Unfortunately, not all patients benefit from the use of these drugs. In addition, neuroleptics may cause significant side effects and they are not efficacious in the therapy of associated behavioral disorders.

In 1988[28] and 1993[12] for the first time two case reports suggested that marijuana smoking improves tics and associated behavioral disorders (e.g., self-mutilatory behavior, attention span, and hypersexuality) in three and one TS patient, respectively. These anecdotal reports were supported by a retrospective survey using a standardized interview.[20] Of 17 patients reporting prior use of marijuana 14 (82 percent) experienced a reduction or complete remission of motor and vocal tics and an amelioration of premonitory urges and obsessive compulsive behavior (OCB).

In an open uncontrolled prospective study[23] in one TS patient, a single-dose treatment with 10 mg delta-9-tetrahydrocannabinol (Δ^9-THC) resulted in an 80 percent improvement of tics. Measuring cognitive functions, neuropsychological tests showed improved signal detection, and sustained attention and reaction time after treatment. The patient himself noted an improvement of motor and vocal tics of about 70 percent and, in addition, felt

an amelioration in attention, impulse control, OCB, and premonitory feeling, without any adverse reactions.

These initial results were confirmed by a randomized double-blind placebo-controlled crossover single-dose trial of Δ^9-THC in 12 adult TS patients.[19,21] Using both self and examiner rating scales, a significant improvement of motor and vocal tics was shown after treatment with Δ^9-THC compared with placebo. In addition, a self rating scale demonstrated a significant improvement of OCB. No serious adverse reactions occurred. Five patients experienced transient mild side effects such as headache, nausea, dizziness, anxiety, sensitivity to noise and light, tiredness, cheerfulness, poor powers of concentration, ataxia, tremble, dry mouth, and hot flush. All these side effects did not last longer than one to six hours. Measuring cognitive functions, neuropsychological tests showed no significant differences after treatment with Δ^9-THC compared with placebo treatment in verbal and visual memory, reaction time, intelligence, sustained and divided attention, vigilance, and mood.

In conclusion, case reports and a randomized study provide evidence that treatment of TS with Δ^9-THC is both effective and safe in the therapy of motor and vocal tics and probably in associated behavioral disorders such as OCB. Evidence suggests that beneficial effects are due to a specific action on central cannabinoid receptors located in basal ganglia and the hippocampus and not due to unspecific mechanisms such as sedation, reduction of anxiety, or the fact of using an illegal drug.[21] Interestingly, neuroanatomical structures which are probably involved in TS pathology, strongly express the CB_1 receptor system. Considering an involvement of the dopamine system in TS pathophysiology it can be speculated that tic improvement might be caused by an interaction between cannabinoid and dopamine mechanisms. To date it is unclear whether the endogenous cannabinoid system is involved in TS pathology. Further studies are needed to confirm these preliminary results.

HUNTINGTON'S DISEASE AND OTHER CHOREIC DISORDERS

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by movement alterations (predominantly chorea but also dystonia, parkinsonism, and ataxia), behavioral changes and impaired cognition. Chorea is characterized by arrhythmic rapid jerky involuntary movements. Neuroanatomically, a selective degeneration of "medium size spiny neurons" in the striatum is evident. In the early course of the disease there is an involvement of striatal GABA/enkephaline neurons projecting to the GPl. Later in the course there is also a degeneration of the GABA-

substance P-containing striatal neurons projecting to the medial globus pallidus (GPm).

Presently, symptomatic treatment with dopamine antagonists (neuroleptics) is the most effective therapy for choreic movements. However, many patients' therapy with neuroleptics is unsatisfactory and limited by side effects.

In 1988 a preliminary report suggested that cannabidiol (CBD) is effective in reducing chorea in HD.[29] However, a placebo-controlled clinical trial in 15 neuroleptic-free patients who received 10 mg CBD/kg per day over a period of six weeks failed to demonstrate efficacy.[3] In an uncontrolled open clinical trial a single-dose treatment of one patient with 1.5 mg nabilone resulted in a marked increase of choreic movements at rest and during movement lasting more than one day.[22]

Considering these preliminary data it seems that in HD, treatment of chorea with cannabinoids is ineffective or even aggravates choreic movements. An explanation for these clinical observations might be that in postmortem studies a massive loss of cannabinoid receptor binding in the SNr[10] and the GPl[25] has been found. Therefore, it can be speculated that an activation of cannabinoid receptors does not enhance GABAergic transmission in the GPl and accordingly does not reduce choreic movements. However, it is unclear whether CB_1 receptors are involved in the pathology of HD and whether the early loss of these receptors contributes to the symptomatology of the disease. It remains unclear which mechanisms caused the marked increase of chorea after treatment with nabilone. To date, there are no studies available investigating whether cannabinoid receptor antagonists might be useful in symptomatic therapy of chorea in HD.

In addition to HD, a variety of other disorders are known which may cause chorea (hereditary choreas, infectious or immunological choreas [including Sydenham's chorea], drug-induced choreas, and metabolic choreas). Choreic movements, regardless of cause, are thought to be caused by a dysfunction in the striatum (caudate and putamen), pallidum, and subthalamic nucleus. Further studies are needed to investigate whether cannabinoids may suppress chorea of other causes.

DYSTONIA

Dystonias are a heterogeneous group of neurological disorders defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures. Dystonia is classified by age of onset, etiology (symptomatic/idiopathic, sporadic/hereditary), and distribution (focal, segmental, hemidystonia, generalized). Dystonia is thought to be a disorder of the basal ganglia, particularly the putamen and the thalamus.

The treatment of dystonia is symptomatic and includes local injections with botulinum toxin type A, anticholinergic drugs, and benzodiazepines. Particularly, the treatment of generalized dystonia remains unsatisfactory in most patients.

In animals, the cannabinoid receptor agonist (+)-WIN 55,212-2 was found to exert antidystonic effects in mutant dystonic hamsters.[26] CBD was found to reduce torticollis in dystonic rats.[4]

In humans, a small number of uncontrolled studies suggested beneficial effects of cannabinoids in dystonia.[6,30,34] In 1984 Snider et al.[34] reported that CBD (200 mg, orally) may be useful in the management of Meige's syndrome (a focal dystonia that involves muscles of facial expression including orbicularis oculi). In 1986 Sandyk et al.[30] found that oral CBD (200 mg) was also effective in symptomatic treatment of spasmodic torticollis (a focal dystonia involving cervical muscles) and of generalized torsion dystonia. In an open uncontrolled trial of CBD in five patients suffering from different forms of dystonia, oral doses of CBD (100 to 600 mg/day, over a period of six weeks) were found to reduce dystonic movements of 20 to 50 percent.[6]

The pharmacology of dystonia is still unknown. Based on theories on the pathophysiology of dystonia, the beneficial effects of CBD might be due to a modulation of GABAergic or glutamatergic neurotransmission resulting in an increased pallidothalamic GABAergic transmission.[7] However, uncontrolled data should be interpreted with caution until results are confirmed by controlled studies.

PARKINSON'S DISEASE AND PARKINSONIAN SYNDROMES

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by bradykinesia, rigidity, resting tremor, and postural instability. Pathophysiologically, it is characterized by a depletion of dopamine in the striatum resulting in an increased inhibitory GABA basal ganglia output. However, the underlying cause of the disease is still unknown. PD has to be differentiated from other parkinsonian disorders which share some clinical features with PD. Parkinsonian syndromes differ in the underlying pathology which is thought to be a decreased density of postsynaptic dopamine receptors. PD and other parkinsonian disorders are summarized as hypokinetic movement disorders.

Therapy of PD is symptomatic including medical treatment and surgical procedures (deep brain stimulation, thalamotomy, pallidotomy). Levodopa is the most effective antiparkinsonian agent known. Other drugs used are dopamine receptor agonists, monoamine oxidase B (MAO-B) and catechol-o-methyltransferase (COMT) inhibitors and anticholinergic agents. In contrast, most patients suffering from parkinsonian syndromes do not respond to

dopaminergic therapy. For most of these disorders no effective treatment is known.

In an open uncontrolled study of CBD in dystonia in two patients with "coexisting parkinsonian features" an exacerbation of hypokinesia and resting tremor was observed while dystonic movements improved.[6] In 1990 an open clinical trial in five patients suffering from PD failed to demonstrate any beneficial effect on tremor or other parkinsonian symptoms when smoking a marijuana cigarette.[9]

However, in 1985 a single case study suggested that CBD may be effective in the management of levodopa-induced dyskinesia in a PD patient.[33] In agreement, in 1998, in a double-blind placebo-controlled crossover study in seven PD patients, it was demonstrated that oral nabilone reduced levodopa-induced dyskinesias without aggravating parkinsonism.[32] In PD, dyskinetic side effects are one of the main problems after prolonged treatment. Dyskinesia is thought to be caused by an overactivity of the GP1. Data obtained from the reserpine-treated rat model of PD suggest that cannabinoids might act to reduce D_2-mediated reductions in GABA release in GPl.[14] Therefore, nabilone may reduce levodopa-induced dyskinesia due to a reduction of GABA reuptake in the GPl.[32]

In summary, evidence suggests that in PD, accompanying treatment with cannabinoids is useful in reducing the complications of dyskinesia after prolonged levodopa therapy without aggravating parkinsonian symptoms.

TREMOR

Tremor is defined as a rhythmical, involuntary oscillatory movement of a body part. It can be classified clinically according to the behavioral circumstances of its occurrence (rest, postural, simple kinetic, and intention tremor) or according to its etiology. Numerous causes of tremor are known, for example PD, parkinsonian syndromes, essential tremor, and cerebellar and midbrain tremor. Different pathways have been proposed as being involved in tremor (cerebral cortex, basal ganglia, midbrain, cerebellum, inferior olive, spinal cord). Pharmacologic treatment of tremor depends on its etiology. In essential tremor, beta-adrenergic blockers and primidone are effective. In most other tremor disorders treatment remains unsuccessful.

Some studies have investigated the effect of cannabinoids on tremor in multiple sclerosis (MS) which is usually classified as a cerebellar tremor (see Chapter 17). In MS patients tremor is a common clinical phenomenon. Results from a questionnaire in 1997 showed that 112 MS patients reported some alleviation of their symptoms including tremor with cannabis use.[5] In 1983 in a placebo-controlled single-blind trial, two of eight MS patients demonstrated an improvement in seriously disabling tremor after Δ^9-THC treatment (5 to 15 mg).[2] In 1989 a single case study of a 30-year-old man

suffering from MS showed an improvement of hand-action tremor while he smoked a marijuana cigarette.[16] In addition, electromagnetic recordings revealed an almost completely abolished hand-and-finger tremor after smoking.

In Parkinson's disease and other parkinsonian syndromes it is unclear whether cannabinoids change resting tremor.[7,9,32]

From the available clinical data it remains unclear whether cannabinoids are useful in reducing tremor. Further studies considering different forms of tremor are needed.

CONCLUSIONS

Central cannabinoid receptors are densely located in the output nuclei of the basal ganglia. Cannabinoids have been found to modulate neurotransmission in the basal ganglia by increasing GABAergic transmission, inhibiting glutamate release, and affecting dopaminergic uptake. Furthermore, evidence suggests that an endogenous cannabinoid tone participates in the control of movements. Therefore, it has been suggested that the central cannabinoid system is involved in the regulation of motor activity and might play a role in the pathophysiology of movement disorders.

During the last few years a small number of clinical trials demonstrated that cannabinoids might be effective in the treatment of movement disorders. Controlled studies suggested that cannabinoids are of therapeutic value in the treatment of tics in Tourette's syndrome and in the reduction of levodopa-induced dyskinesia in Parkinson's disease. Furthermore, evidence suggests that cannabinoids might be useful in the treatment of some forms of tremor and dystonia. Present clinical data do not show serious side effects. To date, it is unclear which of the different cannabinoids (e.g., Δ^9-THC, CBD, nabilone) will be the most effective in the treatment of movement disorders. Cannabinoid receptor antagonists could be useful in the treatment of hypokinetic movement disorders and chorea in HD. However, further controlled studies are needed to confirm these preliminary data.

REFERENCES

1. Bouaboula M, Perrachon S, Milligan L, Canat X, Rinaldi-Carmona M, Portier M, Barth F, Calandra B, Pecceu F, Lupker J, et al. A selective inverse agonist for central cannabinoid receptor inhibits mitogen-activated protein kinase activation stimulated by insulin or insulin-like growth factor 1. Evidence for a new model of receptor/ligand interactions. *Journal of Biological Chemistry* 1997;272(35): 22330-22339.

2. Clifford DB. Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology* 1983;13(6):669-671.

3. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry and Behavior* 1991;40(3):701-708.

4. Consroe P, Musty R, Conti L. Effects of cannabidiol in animal models of neurological functions. In Chester G, Consroe P, Musty R, eds. *Marijuana: An international research report.* National campaign against drug abuse monograph series, no. 7. Canberra: Australian Government Publishing Service, 1988, pp. 147-152.

5. Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 1997; 38(1):44-48.

6. Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience* 1986;30:277-282.

7. Consroe P. Brain cannabinoid systems as targets for the therapy of neurological disorders. *Neurobiology of Disease* 1998;5(6 Pt B):534-551.

8. Crawley JN, Corwin RL, Robinson JK, Felder CC, Devane WA, Axelrod J. Anandamide, an endogenous ligand of the cannabinoid receptor, induces hypomotility and hypothermia in vivo in rodents. *Pharmacology, Biochemistry and Behavior* 1993;46(4):967–972.

9. Frankel JP, Hughes A, Lees AJ, Stern GM. Marijuana for parkinsonian tremor. *Journal of Neurology, Neurosurgery and Psychiatry* 1990;53(5):436.

10. Glass M, Faull RL, Dragunow M. Loss of cannabinoid receptors in the substantia nigra in Huntington's disease. *Neuroscience* 1993;56(3):523-527.

11. Gueudet C, Santucci V, Rinaldi-Carmona M, Soubrie P, Le Fur G. The CB_1 cannabinoid receptor antagonist SR 141716A affects A9 dopamine neuronal activity in the rat. *Neuroreport* 1995;6(10):1421-1425.

12. Hemming M, Yellowlees PM. Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology* 1993;7:389-391.

13. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC. Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States of America* 1990;87(5):1932-1936.

14. Maneuf YP, Crossman AR, Brotchie JM. The cannabinoid receptor agonist WIN 55,212-2 reduces D_2, but not D_1, dopamine receptor-mediated alleviation of akinesia in the reserpine-treated rat model of Parkinson's disease. *Experimental Neurology* 1997;148(1):265-270.

15. Maneuf YP, Nash JE, Crossman AR, Brotchie JM. Activation of the cannabinoid receptor by delta-9-tetrahydrocannabinol reduces gamma-aminobutyric acid uptake in the globus pallidus. *European Journal of Pharmacology* 1996;308(2):161–164.

16. Meinck HM, Schönle PW, Conrad B. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology* 1989;236(2):120-122.

17. Miller AS, Walker JM. Effects of a cannabinoid on spontaneous and evoked neuronal activity in the substantia nigra pars reticulata. *European Journal of Pharmacology* 1995;279(2-3):179-185.

18. Moss DE, Manderscheid PZ, Montgomery SP, Norman AB, Sanberg PR. Nicotine and cannabinoids as adjuncts to neuroleptics in the treatment of Tourette syndrome and other motor disorders. *Life Sciences* 1989;44(21):1521-1525.

19. Müller-Vahl KR, Koblenz A, Jöbges M, Kolbe H, Emrich HM, Schneider U. Influence of delta-9-Tetrahydrocannabinol (Δ^9-THC) treatment of Tourette-syndrome on neuropsychological performance. *Pharmacopsychiatry* 2001;34(1):19-24.

20. Müller-Vahl KR, Kolbe H, Schneider U, Emrich HM. Cannabinoids: Possible role in pathophysiology of Gilles de la Tourette-syndrome. *Acta Psychiatrica Scandinavica* 1998;97:1-5.

21. Müller-Vahl KR, Schneider U, Koblenz A, Jöbges M, Kolbe H, Daldrup T, Emrich HM. Treatment of Tourette-Syndrome with Δ^9-tetrahydrocannabinol (THC). (submitted for publication).

22. Müller-Vahl KR, Schneider U, Emrich HM. Nabilone deteriorates choreatic movements in Huntington's disease. *Movement Disorders* 1999;14:1038-1040.

23. Müller-Vahl KR, Schneider U, Kolbe H, Emrich HM. Treatment of Tourette-syndrome with delta-9-tetrahydrocannabinol. *American Journal of Psychiatry* 1999;156(3):495.

24. Pertwee RG, Wickens AP. Enhancement by chlordiazepoxide of catalepsy induced in rats by intravenous or intrapallidal injections of enantiomeric cannabinoids. *Neuropharmacology* 1991;30(3):237-244.

25. Richfield EK, Herkenham M. Selective vulnerability in Huntington's disease: Preferential loss of cannabinoid receptors in lateral globus pallidus. *Annals of Neurology* 1994;36(4):577-584.

26. Richter A, Loscher W. (+)-WIN 55,212-2, a novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters. *European Journal of Pharmacology* 1994;264(3):371-377.

27. Rodriguez de Fonseca F, Del Arco I, Martin-Calderon JL, Gorriti MA, Navarro M. Role of the endogenous cannabinoid system in the regulation of motor activity. *Neurobiology of Disease* 1998;5(6Pt B):483-501.

28. Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology* 1988;8:444-445.

29. Sandyk R, Consroe P, Snider SR, Bliklen D. Preliminary trial of cannabidiol in Huntington's disease. In Chester G, Consroe P, Musty R, eds. *Marijuana: An international research report.* National campaign against drug abuse monograph series, no. 7. Canberra: Australian Government Publishing Service, 1988, pp. 157-162.

30. Sandyk R, Snider SR, Consroe P, Elias SM. Cannabidiol in dystonic movement disorders. *Psychiatry Research* 1986;18(3):291.

31. Sanudo-Pena MC, Walker JM. Role of the subthalamic nucleus in cannabinoid actions in the substantia nigra of the rat. *Journal of Neurophysiology* 1997;77(3):1635-1638.

32. Sieradzan KA, Fox SH, Dick J, Brotchie JM. The effects of the cannabinoid receptor agonist nabilone on L-DOPA induced dyskinesia in patients with idiopathic Parkinson's disease (PD). *Movement Disorders* 1998;13(Suppl 2):29.

33. Snider SR, Consroe P. Beneficial and adverse effects of cannabidiol in a Parkinson patient with sinemet-induced dystonic dyskinesia. *Neurology* 1985;35(Suppl):201.

34. Snider SR, Consroe P. Treatment of Meige's syndrome with cannabidiol. *Neurology* 1984;34(Suppl):147.

35. Souilhac J, Poncelet M, Rinaldi-Carmona M, Le Fur G, Soubrie P. Intrastriatal injection of cannabinoid receptor agonists induced turning behavior in mice. *Pharmacology, Biochemistry and Behavior* 1995;51(1):3-7.

Chapter 19

Glaucoma and Cannabinoids

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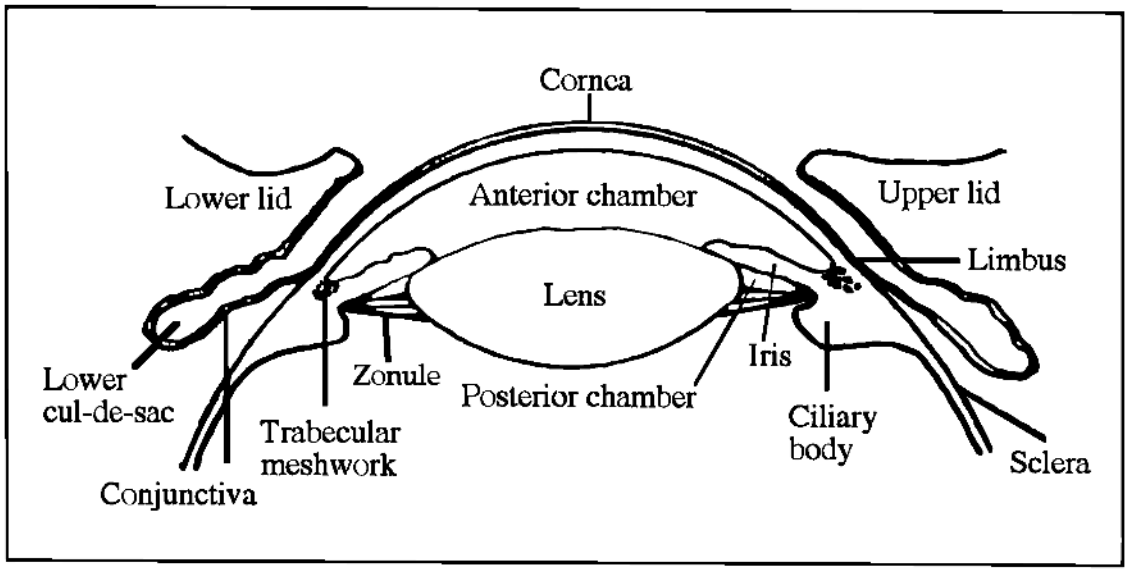
Primary open-angle glaucoma is a chronic ocular disease that is usually characterized by an elevation of intraocular pressure (IOP) caused by inadequate drainage of aqueous humor. This leads to a gradual deterioration of the optic nerve, ultimately resulting in blindness. The ciliary body (see Figure 19.1) is the source of aqueous humor, which initially flows through the posterior chamber, continues via a gap between the iris and lens, and traverses the pupil to the anterior chamber, where it ultimately exits Schlemm's canal. This drainage structure is a 1 to 2 μm diameter channel, concentric with the outer border of the iris and located near its attachment to the anterior section of the ciliary body. It is covered with three layers of the trabecular meshwork (see Figure 19.1), which are structures that serve to filter debris.

The juxtacannular tissue (i.e., cribriform plexus) is the innermost of these meshwork layers and is attached to the inner canal wall. Changes in this layer are critical for development of the ocular hypertension that characterizes primary open-angle glaucoma, the most common type. Unknown hereditary factors (particularly in myopic patients), which involve the meshwork structure (e.g., see the review by Stone et al.[51]) and/or the processes which normally keep it clear, gradually restrict proper aqueous humor flow.

Overpressure resulting from these restrictions is naturally ameliorated through a process called uveoscleral flow. By this route, aqueous humor is conducted via the anterior face of the ciliary body to the venous and lymph drainage of the sclera. Flow between ciliary muscle fiber bundles is possible because this part of the ciliary body does not possess an endothelial layer. In addition, elastic elements serve to maintain these interstitial drainages. This route normally accounts for less than 20 percent of total ocular drainage, as measured in the enucleated eyes of geriatric patients.[3]

FIGURE 19.1. Gross Structure of the Eye



Source: Modified from Suhonen P. Modification of ocular pilocarpine delivery by prodrug derivatization: In vitro and in vivo studies. PhD dissertation, Kuopio University Publications A. Pharmaceutical Sciences 27, 1996.

There is no known cure for glaucoma, but treatment consists of various surgical and pharmaceutical measures that are employed to control the symptomatic ocular hypertension that ultimately leads to blindness. For most people, the latter therapy is used to slow or arrest this course of visual deterioration. A lifetime of drug maintenance is required, usually through the topical application of eyedrops. These compounds act by one of two obvious strategies, a reduction of aqueous humor production or an increase of its outflow, or some combination of the two actions. Pharmacological classes of glaucoma drugs in current use include adrenergic agonists/antagonists, parasympathomimetics, carbonic anhydrase inhibitors, and prostaglandins.[33] All of these drug categories suffer significant drawbacks: incompatibility with certain patient types, side effects of a more or less tolerable nature, and occasional ineffectiveness or eventual loss of effectiveness.

CANNABINOIDS AS OCULAR HYPOTENSIVES

Local Administration

Topical application of cannabinoids to the eye would seem to be the best method for minimizing systemic drug concentrations and maximizing dose at the site of action. However, as cannabinoids are not water soluble, investi-

gations employing several more physically compatible vehicles have been made. These carriers included sesame oil[24] or mineral oil,[16,24,31,39] the latter of which worked best. Unfortunately, mineral oil can be irritating[31] and has been demonstrated to influence IOP itself.[39] Colasanti et al.[7,8,9] employed polyethylene glycol for acute doses as well as chronic administration via osmotic pumps. Use of anandamides (see Chapter 34) or other cannabinoids in aqueous media as water-soluble derivatives,[17] or with the aid of Tween 80,[16] submicron aqueous emulsification,[40] and cyclodextrin-complexes[2] have yielded various degrees of success, although practical application of these discoveries await future development.

Systemic Administration

Discovery of the IOP-lowering properties of THC was originally made by Hepler and Frank[28] through their studies with marijuana smokers. This publication led to a series of confirming studies with both the smoked herb[13,29,37] and pure THC administered via intravenous[10,12,18,20,22,43] or oral[38] routes. Most subjects experienced a reduction of IOP, which averaged approximately 25 to 30 percent. However, it soon became apparent from human studies, that systemic routes of administration carried the burden of significant psychic and minor cardiovascular side effects. In addition, glaucoma is one of the few medical indications for which the application of smoked marijuana evokes a realistic concern of possible long-term pulmonary consequences. This is due to the required combination of frequent inhalation (every two to three hours) of high smoke volumes (several "joints" per day, using 2 percent THC marijuana), administered over the course of a lifetime. Fortunately, the use of modern medical marijuana (10 to 30 percent THC) now allows adequate doses to be delivered with only one or two inhalations. Chronic maintenance on oral marijuana or synthetic THC obviates pulmonary concerns and provides more sustained blood THC levels, particularly during periods of nocturnal inactivity. However, the difficulty of achieving consistent intestinal absorption is well known, and unacceptable psychic disturbances can result.[38]

MECHANISMS OF ACTION

Intraocular Pressure Reduction

The actual mechanism of action for cannabinoid reduction of IOP is unknown. Because smoking marijuana reduces systemic blood pressure, the obvious hypothesis is that any IOP reduction is simply a reflection of this general change. Although somatic hypotension may have such an ocular influence, it probably cannot account for most of the observed IOP effect.[32]

Subsequent to the discovery of ocular prostaglandins in the 1960s and their demonstrated influence on IOP, research indicated that THC interfered with the ocular production of prostaglandin E_2 (PGE_2) from arachidonic acid.[22] Because the direct application of prostaglandins was known to increase ocular hypertension, it was thought that THC might act to interfere with this mechanism. However, because administration of known cyclooxygenase inhibitors (e.g., aspirin, indomethacin) does not affect IOP, this hypothesis seems doubtful.[32]

The presence of a significant contralateral eye effect has also been construed as an indication that control of IOP in general, and the role of the cannabinoids in particular, is mediated through the central nervous system (CNS). Evidence for at least the latter contention is not convincing and is confused by the fact that species differences among test animals influence drug susceptibility and nervous control of IOP. In studies on gangliectomized cats,[6,17] the neurally isolated target eye sometimes provided a diminished response to THC, indicating at least some sympathetic nervous influence on IOP. However, chronic dosing studies in cats[7,8,9] revealed a substantial difference between cannabinoid-treated and untreated eyes, which supports the local effect hypothesis. In addition, Liu and Dacus[34] found that direct administration of THC into the cerebral ventricles of rabbits, or ventriculocisternal perfusion, was without an IOP effect.

Widespread reports of mucosal drying by marijuana users and experimental observations of arterial hypotension led to a suspicion that IOP reduction was due to cannabinoid effects on the adrenergic nervous system. Green and Pederson[21] found a 75 percent reduction in aqueous humor production for the isolated rabbit ciliary body treated with THC, and attributed this to either direct effects on the secretory mechanism or indirect effects on associated vasculature. Reduction of secretion was also accompanied by increased outflow,[18] probably by the uveoscleral route. An *alpha* or *beta* adrenergic antagonist was found to reverse the THC-induced reduction of rabbit IOP by approximately 50 and 100 percent, respectively.[19] The former drug also inhibited the THC-induced increase in total outflow facility. Crosson and Gray[11] have demonstrated the IOP influence of noncannabinoid adenosine agonists on rabbits and attributed the hypotensive effects to suppression of iris/ciliary body adenylate cyclase and cAMP through a negative coupling to the $alpha_1$ receptor. THC can also act as a monoamine oxidase inhibitor[47] and through this indirect mechanism, possibly raise levels of endogenous ocular catecholamines.[14] Apparently, various inputs may influence the IOP effects of cannabinoids, probably through competing mechanisms. However, Colasanti[5] has concluded, on the basis of her own experiments with cats, and a comprehensive literature review, that a CNS-independent outflow facility increase of up to threefold is the major mechanism by which cannabinoid-induced hypotension occurs.

The discovery that topical anandamides affect IOP (see Chapter 34) has stimulated the search for an ocular cannabinoid receptor. Sugrue et al.[56] also found evidence of possible local activity, as well as enantioselectivity, for other topically applied ophthalmic cannabinoids. Porcella et al.[44] discovered RT-PCR evidence of CB_1 receptors in ciliary body areas of the rat eye appropriate for control of IOP via such a mechanism, and Straiker et al.[52,53] recently reported similar results in the human eye. These preliminary works provide physio-anatomical support for the contention of a localized and receptor-specific cannabinoid IOP effect.

Neurological Implications

IOP is only one factor in the pathophysiology of glaucoma, and its influence on the retinal disk is indirect. Damage to this site is thought to occur through at least two mechanisms: occlusion of axonal flow, which causes localized interference with delivery of organelles[30] and cytosolic factors;[42] and restriction of the microcirculation that nourishes the nerve.[45] Although both phenomena are influenced by IOP, the latter may also occur independently. Indeed, a significant percentage of glaucoma patients exhibit normotensive IOP. This pathology may originate from a circulatory deficit caused or exacerbated by the presence of excess endogenous vasoconstrictive agents such as endothelin-1 or nitric oxide.[25] The presence of CB_1-type receptors in vascular tissues[15] and the demonstrated ability of anandamide,[58] 2-arachidonylglycerol,[55] and THC[23] to induce vasodilation, implies a mechanism by which such a circulatory deficit might be counteracted. Other cannabinoids act in this fashion, and their antioxidant (see Chapter 9) and NMDA receptor properties (see Chapter 36) could also indirectly influence microcirculation, as well as IOP, by affecting ocular nitric oxide[25] and calcium ion levels,[15] respectively.

On the intracellular level, retinal disk ischemia causes anoxia and hypoglycemia, resulting in neuronal toxicity and ultimately inducing the form of genetically programmed "suicide" known as apoptosis.[42] This, in turn, contributes to a toxic extracellular environment which may result in an ongoing progression of optic nerve degeneration.[48] The secondary neuronal injury observed in stroke or head trauma patients and various neurodegenerative disorders acts by a similar mechanism (see Chapters 9 and 36). Among the products produced by this process are an excess of neurotransmitters such as glutamate[54] and nitric oxide.[1]

The nonpsychoactive synthetic cannabinoid HU-211, which is essentially an enantiomer of the major Δ^8-THC metabolite, has been investigated for its utility in both secondary brain and optic nerve[48] injury. Calcium channel blockers have shown promise for clinical use in glaucoma,[41] and the ability of HU-211 to antagonize NMDA receptor activity is complimentary. Interestingly, anandamide has demonstrated an ability to modulate this

receptor[26] and palmitylethanolamide has also been shown to exhibit an indirect antiexcitotoxic effect involving the CB_2 receptor.[50] Tumor necrosis factor *alpha* has been suggested[49] as a primary mediator of neurotoxicity after brain trauma, and its possible involvement in retinal ischemia also bears scrutiny. The antioxidant properties of THC or CBD are similar to those of HU-211,[27] and cannabinoids can attenuate a CB_1 receptor mediated production of nitric oxide,[59] possibly ameliorating apoptosis as well as free radical toxicity. The oxidative effect of dopamine on apoptosis has been noted,[35] and its regulation by cannabinoids has been demonstrated by Schlicker et al.[46] in the guinea pig retinal disk. An equivalent endogenous process might be inferred from recently reported anandamide synthesis and catabolism in the retina,[4,36] as well as the discovery of retinal CB_1 receptors.[44,52,53]

The overall implication for the sum of these studies is potentially significant. Cannabinoids may reveal themselves to be useful for the treatment of glaucoma in a quite comprehensive manner: lowering IOP, restoring microcirculation, inhibiting apoptosis, and minimizing free radical damage. This hypothetical multiple mechanism would surpass that employed by any current ocular drug, and may help to explain why the use of marijuana has preserved the sight of those unresponsive to other glaucoma therapies.

REFERENCES

1. Adachi K, Fujita Y, Morizane C, Akaike A, Ueda M, Satoh M, Masai H, Kashii S, Honda Y. Inhibition of NMDA receptors and nitric oxide synthase reduces ischemic injury of the retina. *European Journal of Pharmacology* 1998; 350(1):53-57.

2. Arsenovic J. Formulation of aqueous ophthalmic solutions of cannabinoids for use in glaucoma therapy. MPh thesis, University of Otago, Dunedin, New Zealand, 1997.

3. Bill A, Phillips CI. Uveoscleral drainage of aqueous humor in human eyes. *Experimental Eye Research* 1971;12(3):275-281.

4. Bisogno T, Delton-Vandenbroucke I, Milone A, Lagarde M, Di Marzo V. Biosynthesis and inactivation of *N*-arachidonoyl-ethanolamine (anandamide) and *N*-docosahexaenoyl-ethanolamine in bovine retina. *Archives of Biochemistry and Biophysics* 1999;370(2):300-307.

5. Colasanti BK. Review: Ocular hypotensive effect of marihuana cannabinoids: Correlate of central action or separate phenomenon? *Journal of Ocular Pharmacology* 1986;2(3):295-304.

6. Colasanti BK. A comparison of the ocular and central effects of Δ^9-tetrahydrocannabinol and cannabigerol. *Journal of Ocular Pharmacology* 1990; 6(4):259-269.

7. Colasanti BK, Brown RE, Craig CR. Ocular hypotension, ocular toxicity, and neurotoxicity in response to marijuana extract and cannabidiol. *General Pharmacology* 1984;15(6):479-484.

8. Colasanti BK, Craig CR, Allara RD. Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol. *Experimental Eye Research* 1984;39(3):251-259.

9. Colasanti BK, Powell SR, Craig CR. Intraocular pressure, ocular toxicity and neurotoxicity after administration of Δ^9-tetrahydrocannabinol or cannabichromene. *Experimental Eye Research* 1984;38(1):63-71.

10. Cooler P, Gregg JM. The effect of delta-9-tetrahydrocannabinol on intraocular pressure in humans. *Southern Medical Journal* 1977;70(8):951-954.

11. Crosson CE, Gray T. Modulation of intraocular pressure by adenosine agonists. *Journal of Ocular Pharmacology* 1994;10:379-383.

12. ElSohly MA, Harland EC, Benigni DA, Waller CW. Cannabinoids in glaucoma II: The effect of different cannabinoids on intraocular pressure of the rabbit. *Current Eye Research* 1984;3(6):841-850.

13. Flom MC, Adams AJ, Jones RT. Marijuana smoking and reduced intraocular pressure in human eye: Drug action or epiphenomenon? *Investigative Ophthalmology* 1975;14(1):52-55.

14. Gawienowski AM, Chatterjee D, Anderson PJ, Epstein DL, Grant WM. Effect of Δ^9-tetrahydrocannabinol on monoamine oxidase activity in bovine eye tissues, in vitro. *Investigative Ophthalmology and Visual Science* 1982;22(4):482-485.

15. Gebremedhin D, Lange AR, Campbell WB, Hilliard CJ, Harder DR. Cannabinoid CB_1 receptor of cat cerebral arterial muscle functions to inhibit L-type Ca^{2+} channel current. *American Journal of Physiology* 1999;276(6 Pt 2):2085-2093.

16. Green K, Bigger JF, Kim K, Bowman K. Cannabinoid penetration and chronic effects in the eye. *Experimental Eye Research* 1977;24(2):197-205.

17. Green K, Bigger JF, Kim K, Bowman K. Cannabinoid action on the eye as mediated through the central nervous system and local adrenergic activity. *Experimental Eye Research* 1977;24(2):189-196.

18. Green K, Bowman K. Effect of marihuana and derivatives on aqueous humor dynamics in the rabbit. In Braude MC, Szara S, eds. *The pharmacology of marihuana*. New York: Raven Press, 1976, Volume 2, pp. 803-813.

19. Green K, Kim K. Mediation of ocular tetrahydrocannabinol effects by adrenergic nervous system. *Experimental Eye Research* 1976;23(4):443-448.

20. Green K, Pederson JE. Effect of Δ^9-tetrahydrocannabinol on aqueous dynamics and ciliary body permiability in the rabbit. *Experimental Eye Research* 1973;15(4):499-507.

21. Green K, Pederson JE. Aqueous humor formation. *Experimental Eye Research* 1973;16(4):273-286.

22. Green K, Podos SM. Antagonism of arachidonic acid-induced ocular effects by Δ^9-tetrahydrocannabinol. *Investigative Ophthalmology* 1974;13(6):422-429.

23. Green K, Wynn H, Padgett D. Effects of Δ^9-tetrahydrocannabinol on ocular blood flow and aqueous humor formation. *Experimental Eye Research* 1978;26(1):65-69.

24. Green K, Wynn H, Bowman KA. A comparison of topical cannabinoids on intraocular pressure. *Experimental Eye Research* 1978;27(2):239-246a.

25. Haefliger IO, Dettmann E, Liu R, Meyer P, Prunte C, Messerli J, Flammer J. Potential role of nitric oxide and endothelin in the pathogenesis of glaucoma. *Survey of Ophthalmology* 1999;43(Suppl 1):51-58.

26. Hampson AJ, Bornheim LM, Scanziani M, Yost CS, Gray AT, Hansen BM, Leonoudakis DJ, Bickler PE. Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission. *Journal of Neurochemistry* 1998;70(2): 671-676.

27. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)-Δ^9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95(14):8268-8273.

28. Hepler RS, Frank IM. Marihuana smoking and intraocular pressure. *Journal of the American Medical Association* 1971;217(10):1392.

29. Hepler RS, Frank IM, Petrus R. Ocular effects of marijuana smoking. In Braude MC, Szara S, eds. *The pharmacology of marihuana*. New York: Raven Press, 1976, Volume 2, pp. 815-828.

30. Hohmann AG, Herkenham M. Cannabinoid receptors undergo axonal flow in sensory nerves. *Neuroscience* 1999;92(4):1171-1175.

31. Jay WM, Green K. Multiple-drop study of topically applied 1 percent Δ^9-tetrahydrocannabinol in human eyes. *Archives of Ophthalmology* 1983;101(4):591-593.

32. Korczyn AD. The ocular effects of cannabinoids. *General Pharmacology* 1980;11(5):419-423.

33. Leino M, Urtti A. Recent developments in anti-glaucoma research. In Reddy IK, ed. *Ocular therapeutics and drug delivery*. Lancaster, PA: Technomic Publishing, 1996, pp. 245-264.

34. Liu JHK, Dacus AC. Central nervous system and peripheral mechanisms in ocular hypotensive effect of cannabinoids. *Archives of Ophthalmology* 1987;105(2): 245-258.

35. Luo Y, Umegaki H, Wang X, Abe R, Roth GS. Dopamine induces apoptosis through an oxidation-involved SAPK/JNK activation pathway. *Journal of Biological Chemistry* 1998;273(6):3756-3764.

36. Matsuda S, Kanemitsu N, Nakamura A, Mimura Y, Ueda N, Kurahashi Y, Yamamoto S. Metabolism of anandamide, an endogenous cannabinoid receptor ligand, in porcine ocular tissues. *Experimental Eye Research* 1997;64(5):707-711.

37. Merritt JC, Crawfford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology* 1980;81(3):222-228.

38. Merritt JC, McKinnon S, Armstrong JR, Hatem G, Reid LA. Oral Δ^9-tetrahydrocannabinol in heterogenous glaucomas. *Annals of Ophthalmology* 1980;12:947-950.

39. Merritt JC, Shrewsbury RP, Locklear F, Demby KB, Wittle GL. Effects of Δ^9-tetrahydrocannabinol and vehicle constituents on intraocular pressure in normotensive dogs. *Research Communications in Substance Abuse* 1986;7:29-35.

40. Muchtar S, Almog S, Torracca MT, Saettone MF, Benita S. A sub-micron emulsion as ocular vehicle for delta-8-tetrahydrocannabinol: Effect on intraocular pressure in rabbits. *Ophthalmic Research* 1992;24(3):142-149.

41. Netland PA, Chaturvedi N, Dreyer EB. Calcium channel blockers in the management of low-tension and open-angle glaucoma. *American Journal of Ophthalmology* 1993;115(5):608-613.

42. Nickells RW, Zack DJ. Apoptosis in ocular disease: A molecular overview. *Ophthalmic Genetics* 1996;17(4):145-165.

43. Perez-Reyes M, Wagner D, Wall ME, Davis KH. Intravenous administration of cannabinoids and intraocular pressure. In Braude MC, Szara S, eds. *The pharmacology of marihuana*. New York: Raven Press, 1976, Volume 2, pp. 829-832.

44. Porcella A, Casellas P, Gessa GL, Pani L. Cannabinoid receptor CB_1 mRNA is highly expressed in the rat ciliary body: Implications for the antiglaucoma properties of marihuana. *Brain Research. Molecular Brain Research* 1998;58(1-2):240-245.

45. Prunte C, Orgul S, Flammer J. Abnormalities of microcirculation in glaucoma: Facts and hints. *Current Opinion in Ophthalmology* 1998;9(2):50-55.

46. Schlicker E, Timm J, Gothert M. Cannabinoid receptor-mediated inhibition of dopamine release in the retina. *Naunyn-Schmiedebergs Archives of Pharmacology* 1996;354(6):791-795.

47. Schurr A, Rigor BM. Monoamineoxidase and cannabis: Species, tissue and drug selectivity. In Agurell S, Dewey WL, Willette RE, eds. *The cannabinoids: Chemical, pharmacologic, and therapeutic aspects*. New York: Academic Press, 1984, pp. 603-620.

48. Schwartz M, Yoles E. Optic nerve degeneration and potential neuroprotection: Implications for glaucoma. *European Journal of Ophthalmology* 1999;9(Suppl. 1): 9-11.

49. Shohami E, Gallily R, Mechoulam R, Bass R, Ben-Hur T. Cytokine production in the brain following closed head injury: Dexanabinol (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant. *Journal of Neuroimmunology* 1997;72(2):169-177.

50. Skaper SD, Buriani A, Dal-Toso R, Petrelli L, Romanello S, Facci L, Leon A. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proceedings of the National Academy of Sciences of the United States of America* 1996;93(9):3984-3989.

51. Stone EM, Fingert JH, Alward WLM, Nguyen TD, Polansky JR, Sunden SLF, Nishimura D, Clark AF, Nystuen A, Nichols BE, et al. Identification of a gene that causes primary open angle glaucoma. *Science* 1997;275(5300):668-670.

52. Straiker AJ, Maguire G, Mackie K, Lindsey J. Localization of cannabinoid CB_1 receptors in the human anterior eye and retina. *Investigative Ophthalmology and Visual Science* 1999;40(10):2442-2448.

53. Straiker A, Stella N, Piomelli D, Mackie K, Karten HJ, Maguire G. Cannabinoid CB_1 receptors and ligands in vertebrate retina: Localization and function of an endogenous signaling system. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96(25):14565-14570.

54. Sucher NJ, Lipton SA, Dreyer EB. Molecular basis of glutamate toxicity in retinal ganglion cells. *Vision Research* 1997;37(24):3483-3493.

55. Sugiura T, Kodaka T, Nakane S, Kishimoto S, Kondo S, Waku K. Detection of an endogenous cannabimimetic molecule, 2-arachidonoylglycerol, and cannabinoid CB_1 receptor mRNA in human vascular cells: Is 2-arachidonoylglycerol a possible vasomodulator? *Biochemical and Biophysical Research Communications* 1998; 243(3):838-843.

56. Sugrue MF, Funk HA, Leonard Y, O'Neill-Davis L, Labelle M. The ocular hypotensive effects of synthetic cannabinoids. *Investigative Ophthalmology and Visual Science* 1997;37:831.

57. Suhonen P. Modification of ocular pilocarpine delivery by prodrug derivatization: In vitro and in vivo studies. PhD Dissertation, Kuopio University Publications A. Pharmaceutical Sciences 27, 1996.

58. Wagner JA, Varga K, Jarai Z, Kunos G. Mesenteric vasodilation mediated by endothelial anandamide receptors. *Hypertension* 1999;33(1 Pt 2):429-434.

59. Waksman Y, Olsen JM, Carlisle SJ, Cabral GA. The central cannabinoid receptor (CB_1) mediates inhibition of nitric oxide production by rat microglial cells. *Journal of Pharmacology and Experimental Therapeutics* 1999;288(3):1357-1366.

Chapter 20

Dependency and Cannabis

Tod H. Mikuriya

PRE-PROHIBITION

In 1839 William B. O'Shaughnessy[18] visited cannabis buyers' centers in India and mingled with the "dissolute and depraved" to learn about the preparations of this social drug for clinical medical trials and found it to be useful in the treatment of tetanus and seizures (see Chapter 4).

Cannabis Substitution for Other Addictive Drugs

In 1843 Clendinning[4] utilized cannabis substitution for the treatment of alcoholism and opium addiction. Potter recommended full-dose Squibb cannabis extract for withdrawal from opium addiction.[19]

In 1894 the Indian Hemp Drugs Commission Report recognized the comparative safety of cannabis in its unsurpassed ethnographic studies within different cultures with a concern that if prohibited it would cause the use of more dangerous drugs.[8]

Cannabis in Combination with Other Medicines

McMeens, citing Fronmueller in 1860,[13] found that the use of cannabis in place of, or combined with, opiates reduced harm from increased dose, tolerance, dependence, and side effects of opiates. In 1867, cannabis was confirmed as useful in the treatment of delirium tremens and as an alternative to opium for analgesia.[20] Dutt independently described the comparative safety of cannabis in *Materia medica of the Hindus*.[6] Yeo and colleagues warned about addiction to morphine in the treatment of neuralgia and suggested cannabis as an alternative.[23]

CANNABIS AND MOOD DISORDERS

The connection between dependency on drugs and mood disorders may be caused by unsuccessful attempts to self-medicate uncomfortable feelings with the "cure," causing more harm and aggravation of the underlying condition. Moreau described cannabis as being useful in the treatment of depression in 1845.[17] Throughout the late nineteenth and early twentieth centuries, the drug was listed in medical texts and pharmaceutical catalogues for treatment of melancholia or mania.[10,14,21,5]

According to interviews with patients who use cannabis medicinally, some of them report that cannabis facilitates both antimania and antidepressant medications (see Table 12.2 in Chapter 12). Cannabis used in combination with selective serotonin reuptake inhibitors (SSRI-type antidepressants) appears to decrease the side effects of nervousness, muscle tension, and nausea. Other patients report that cannabis is complementary. A typical report is that SSRIs elevate mood overall and cannabis improves affectual responsivity. Cannabis can either diminish the dosage needs for sufferers of bipolar disorders or substitute altogether for antimania medications. With symptoms of mania or agitation, cannabis appears to decrease affectual lability. Cannabis's restoration of sleep without "hangover" also plays an important therapeutic role in detoxification and treatment. Wakefulness can be calmed by one or two inhalations.

CANNABIS SUBSTITUTION FOR MORE HARMFUL NONMEDICAL DRUGS

Notwithstanding some polysubstance abusers who maladaptively combine cannabis with other psychoactives, there appears to be a significant number of persons who have learned that cannabis can totally substitute for other psychoactive drugs.

Following the therapeutic paths of Clendinning, throughout the nineteenth and early twentieth century, cannabis was found useful in the treatment of opiate and sedative abuse. Brunton described the use of cannabis for the treatment of opiate dependence or as a substitute when opiates were not tolerated.[3] Shoemaker found cannabis to be used for the cure of opium or chloral habits.[21] Birch advocated for the use of Indian hemp in the treatment of chronic chloral and opium poisoning.[1] Mattison, an early addiction specialist, recommended cannabis as a substitute for morphine and cautioned his fellow physicians about hypodermic use of the opiate.[11]

Alcohol abuse, stimulant, sedative, and opioid abuse and dependence are conditions potentially treatable with cannabis substitution. All of these conditions involve management of mood and emotional reactivity. Although there have been numerous synthetic homologues developed, short-acting

psychotropic drugs continue to have high potential for dependency and abuse. The quality of immediacy for mood management would appear to be inseparable from abuse potential but cannabis appears to be the exception because of lesser or milder withdrawal symptoms.

California cannabis center members and patients in my private practice[16] independently rediscovered and confirmed that cannabis is a safer substitute for many prescribed and most nonmedical psychoactive drugs in the control of depression, anger, and anxiety. Cannabis substitution may be a gateway drug back to sobriety and dealing with the underlying psychopathologic etiologies.

Gieringer, in a report summarizing 2,480 California cannabis users[7] (see also Chapter 12), noted that 5.5 percent (136) described the use of cannabis to be less harmful than alcohol, opiates, and other substances for drug dependency as primary presenting illness. This group of self-medicators found that cannabis caused far fewer adverse effects than opioids, sedatives, and stimulants. This small percentage is for dependency as primary presenting illness and grossly underreports dependencies in chronic pain conditions.

Antabuse (Disulfiram) and Alcoholism

I have personally successfully treated two patients suffering severe alcoholism with a combination of disulfiram and cannabis substitution. This "carrot and stick" approach appears to address the needs of pharmacologic management of mood and avoids relapse during emotionally stressful events.[15]

CANNABIS USE IN TREATMENT OF PSYCHOLOGICAL AND EMOTIONAL TRAUMA

Adult children of alcoholic families are doubly harmed by alcohol abuse and functional disability. Physical and sexual abuse, or emotional absence by one or both parents is compounded by parental failure to provide coping skills to deal with normal feelings and pathologic role models. Alcoholism and polysubstance dependence is significant in those with destructive and symbiotic family involvements.

Vietnam veterans and other survivors of horrific experiences of childhood and adulthood suffer from living nightmares and flashbacks triggered by certain specific stimuli which cause overwhelming "fight or flight" reactions. Chronic depression with insomnia and fearfulness frequently incapacitate and isolate.

In my private practice I have noticed that some patients with post-traumatic stress disorders have come to realize that cannabis is less toxic or harmful than alcohol, opioids, and other psychotropics in their continuing

struggles with indelible memories and their physiologic concomitants. They use cannabis to decrease emotional overreactivity, and to relieve depression and sleep deficit. The use of cannabis by the inhaled route permits the modulation of affectual response without unwanted side effects. Capability for empathetic interpersonal interactions is restored.

Cannabis, unlike other recreational or nonmedical drugs such as alcohol, opiates, cocaine, or amphetamines does not grossly interfere with vegetative functions or circadian rhythms. Substitution, therefore, is therapeutic as it permits restoration of psychophysical normalcy. For others, however, cannabis use can be problematic (see Chapter 27).

Cannabis abuse and dependence appears to be secondary to a pathologic overmodulation or suppression of affectual response in some users which results in alienation and insensitivity to others. The empathetic emotional feedback mechanism impaired in those experiencing difficulty with cannabis use is noted in observations at a Marijuana Anonymous Group.[2] Organized with the same structure as Alcoholics Anonymous, the group came together because of dissatisfaction with AA. A typical complaint was the dismissive attitude toward problems discontinuing the use of cannabis compared with efforts to combat the more addictive alcohol.

The alternative medical movement represents a populist rebellion against conventional medicine in treating chronic relapsing illness including alcohol and other drug dependencies. Cannabis self-medication has been discovered to be a viable alternative to treat these conditions and may enhance or substitute for conventional pharmacotherapy.

DRUG POLICY, DEPENDENCIES, AND CANNABIS

The complex interplay of cannabis use with physiology, psychology, and groups challenges research. Outcomes are a combination of pharmacology, expectations, setting and personal and social forces. The contemporary ambiguity, a product of ignorance from deprivation of contemporary clinical experience, may be somewhat assuaged by two facts: First cannabis has been used for millennia by numerous cultures without serious adverse consequences.[9] Second, neither the composition of cannabis nor the physiology of humans have changed since the drug was taken from the armamentarium of medicine.

Perceptions of cannabis and its effects distorted by sixty years of prohibition are embedded in official U.S. policies.[12] The demonization and persecution of physicians and narcotic addicts they sought to treat significantly limited treatment.[22] Methadone maintenance programs, for the treatment of heroin addiction, remain heavily bureaucratized and functionally rationed in many countries. Alcohol and drug dependency treatment programs remain frequently unavailable, the last to be funded, and the first to be cut

from public budgets and often not covered by private insurance. Drug dependencies should be treated as medical and psychiatric problems and not defined as moral defects. Dependency treatment programs must adequately assess patients to develop individual treatment programs for effectively treating chronic, relapsing illnesses.

REFERENCES

1. Birch EA. The use of Indian hemp in the treatment of chronic chloral and chronic opium poisoning. *Lancet* 1889;1. Reprint in Mikuriya TH, ed. *Marijuana: Medical papers 1839-1972*. Oakland, CA: Medi-Comp Press, 1973.

2. Boyle L. Marijuana Anonymous Group Observations. Personal correspondence, 1989.

3. Brunton TL. *A text book of pharmacology, therapeutics, and materia medica*. Lea Brothers and Co., 1888, pp. 1026-1027.

4. Clendinning J. Observations on the medicinal properties of the *Cannabis sativa* of India. *Medical Chirurgical Transactions,* London 1843;26:188-210.

5. *Dispensatory of the United States of America*. Twentieth Edition, Philadelphia: JB Lippincott Co., 1920, pp. 276-281.

6. Dutt UC. *Materia medica of the Hindus*. Calcutta: Thacker, Spink and Co., 1877, pp. 235-241.

7. Gieringer D. Medical uses of cannabis in California. *Journal of Cannabis Therapeutics* 2000.

8. *Indian Hemp Drugs Commission Report*. Volume 1, Chapter X, Section 490, 1893-1894.

9. *Indian Hemp Drugs Commission Report*. Volume 1, Simla, Chapter X, Effects—General Observations, 1893-1894.

10. Lilly's Bulletin No. 18, p. 1, 1892.

11. Mattison JB. Cannabis as an anodyne and hypnotic. *St. Louis Medical Surgical Journal* LXVI(5) Nov. 1891. Reprint in Mikuriya TH, ed. *Marijuana: Medical papers 1839-1972*. Oakland,CA: Medi-Comp Press, 1973.

12. McCaffrey BR. Federal response to California's passage of Proposition 215. Press conference and related documents, December 30, 1996.

13. McMeens RR. Ohio State Medical Committee on *Cannabis indica*. Transactions of the fifteenth annual meeting of the Ohio State Medical Society, June 12-14, pp. 75 -100. Reprint in Mikuriya TH, ed. *Marijuana: Medical papers 1839-1972*. Oakland,CA: Medi-Comp Press, 1973.

14. *Merck's Index* 1896.

15. Mikuriya TH. Cannabis substitution. An adjunctive therapeutic tool in the treatment of alcoholism. *Medical Times* 1970;98(4):187-191.

16. Mikuriya TH. Medical uses in California. In *1999 Symposium on the Cannabinoids*. Burlington, VT: International Cannabinoid Research Society, 1999, p. 89.

17. Moreau J-J. *Hashish and mental illness*. Peters H, Nahas GG, eds. Translated by Barnett GJ. NY: Raven Press, 1973.

18. O'Shaughnessy WB. On the preparations of the Indian hemp or gunjah *(Cannabis indica)*. Their effects on the animal system in health and their utility in the treatment of tetanus and other convulsive diseases. *Transactions of the Medical and Physical Society of Bengal* 1838-1840, pp. 421-461. Reprint in Mikuriya TH, ed. *Marijuana: Medical papers 1839-1972*. Oakland, CA: Medi-Comp Press, 1973.

19. Potter SOL. *Handbook of materia medica, pharmacy, and therapeutics*. Philadelphia: P Blakiston, Son and Co., 1895, pp. 664-665.

20. Royle JF, Headland FW. *A manual of materia medica and therapeutics*. Fifth Edition. London, 1867, pp. 639-643.

21. Shoemaker JV. *Materia medica and therapeutics*. Philadelphia: FA Davis Co, 1906, p. 305-308.

22. Williams HS. *Drug addicts are human beings. The story of our billion dollar drug racket how we created it and how we can wipe it out*. Washington, DC: Shaw Publishing Co., 1938, p. 273.

23. Yeo IB, Crawfurd R, Buzzard EF. *A manual of medical treatment and clinical therapeutics*. Volume II, New York: William Wood and Co., 1899, pp. 320-321.

PART IV:
RISKS AND SIDE EFFECTS

Chapter 21

Review of Unwanted Actions of Cannabis and THC

Franjo Grotenhermen

The acute effects of cannabis and Δ^9-THC are well established. Concerning chronic effects, some uncertainties exist which give rise to controversy, especially with regard to its long-term effects on psyche and cognition, hormonal effects and reproduction, and the immune system.

This controversy revolves around two aspects:

1. There are conflicting assessments concerning extrapolation and transferability of results of animal and cell studies to human consumption. Hollister pointed out that "virtually every drug that has been studied for dysmorphogenic effects has been found to have them if the doses are high enough, if enough species were tested, or if treatment is prolonged (p. 4)."[17]
2. Since long-term effects in humans are apparently minor, various authors may choose to emphasize existence of such effects ("Marijuana exerts harmful effects . . ."), while others assume their insignificance (". . . but they are minor"). Different conclusions are then reached with regard to therapeutic use.

A widely accepted opinion has been expressed in the report of the U.S. Institute of Medicine of 1999 on the medical use of marijuana: "Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications" (p. 126).[20]

Due to the wide spectrum of cannabis activity, the qualitative evaluation of a specific effect also depends on the expectations of the user. For exam-

ple, an increase of weight while on cannabis therapy due to increased appetite may be welcome or undesirable. The same may be true for effects on psyche, muscle tone, immune system, heart, and circulation. Various reviews on side effects have been published.[9,10,12,17,18,20,32]

OVERALL TOXICITY

The acute toxicity of Δ^9-THC is low. Death due to cannabis has not been observed. The median lethal dose (LD_{50}) of oral THC in rats was 800 to 1900 mg/kg depending on sex and strain.[29]

No cases of death due to toxicity were observed following the maximum THC dose in dogs (up to 3,000 mg/kg THC) and monkeys (up to 9,000 mg/kg THC).[29] Acute fatal cases in humans have not been substantiated. Even a long-term high-dose therapy has been tolerated well. Thus, Chan et al. (1996) administered 50 mg/kg THC to rats for a period of two years.[4] At the end of the observation, overall survival was higher in the treated animals (70 percent) than in the untreated controls (45 percent). The higher survival rate in the THC group was ascribed to the lower incidence of cancer.

No relationship between heavy cannabis use and human mortality has been discovered,[28] although this may possibly be ascribed to methodic limitations of prevailing epidemiological studies.

In an anonymous survey of 128 participants in Germany, Switzerland, and Austria on the medical use of dronabinol and natural cannabis products, 71 percent reported no side effects, 26 percent reported moderate effects, and 3 percent reported severe problems.[27] The overall judgment of "no side effects" had been stated in some cases in which certain side effects (e.g., dry mouth or anxiety) had been previously described by the participants. Apparently, these side effects were regarded as minor. Nearly the same distribution was found for intensity of withdrawal symptoms. Concerning development of tolerance, the following were noted: 84 percent did not have to increase their therapeutic dose within the prior three months, 11 percent had to increase it moderately, and 5 percent had to increase heavily to obtain the desired effects.

ACUTE EFFECTS

Acute effects of cannabis mainly pertain to psyche, cognition, psychomotor performance, and circulation (see Chapters 5 and 22).

Psyche, Cognition, and Psychomotor Performance

Cannabis intoxication is usually described as a pleasant and relaxing experience. Use in a social context may result in laughter and talkativeness.

Occasionally, unpleasant feelings such as anxiety may occur that may escalate to panic. Fear of death is a characteristic feeling in the case of overdose. A sense of enhanced well-being may alternate with dysphoric phases. In an idiosyncratically variable manner, activating effects may be followed by a phase of sedation, occasionally with sleep induction. Strong psychopathological reactions are rare even in case of heavy use.

Psychic effects, such as enhancement of sensory perception, seem to show great variability. According to a study in 345 American students, marijuana use increased sexual desire more often in women than in men (58 percent versus 39 percent).[23] However more men than women reported enhancement of sexual enjoyment (60 percent versus 43 percent).

Cannabis and THC may impair memory, attention, reaction time, motor performance and coordination, decreasing the ability to manage cognitive and motor tasks, for example, driving a car. Tolerance to these effects develops with chronic administration (see Chapter 23).

Physical Effects

Acute physical effects include hyposalivation with dry mouth and throat (atropine-like effect), increased heart rate, conjunctival injection, decrease of tear flow, possible orthostatic hypotension with tendency to fall, seldom with syncope, and increase of blood pressure while lying down. Heart rate increases by 20 to 50 percent, leading to an increase in cardiac labor and oxygen demand, which may be of relevance in patients with severe heart disease (see Figure 21.1). Tolerance is developed within a few days particularly to circulatory effects. Chronic users may demonstrate bradycardia. Rarely, headache or nausea and vomiting may occur after cannabis use. Hyposalivation and decreased tear flow may potentially increase the risk of infections of the upper respiratory tract and the eye (keratitis, conjunctivitis).

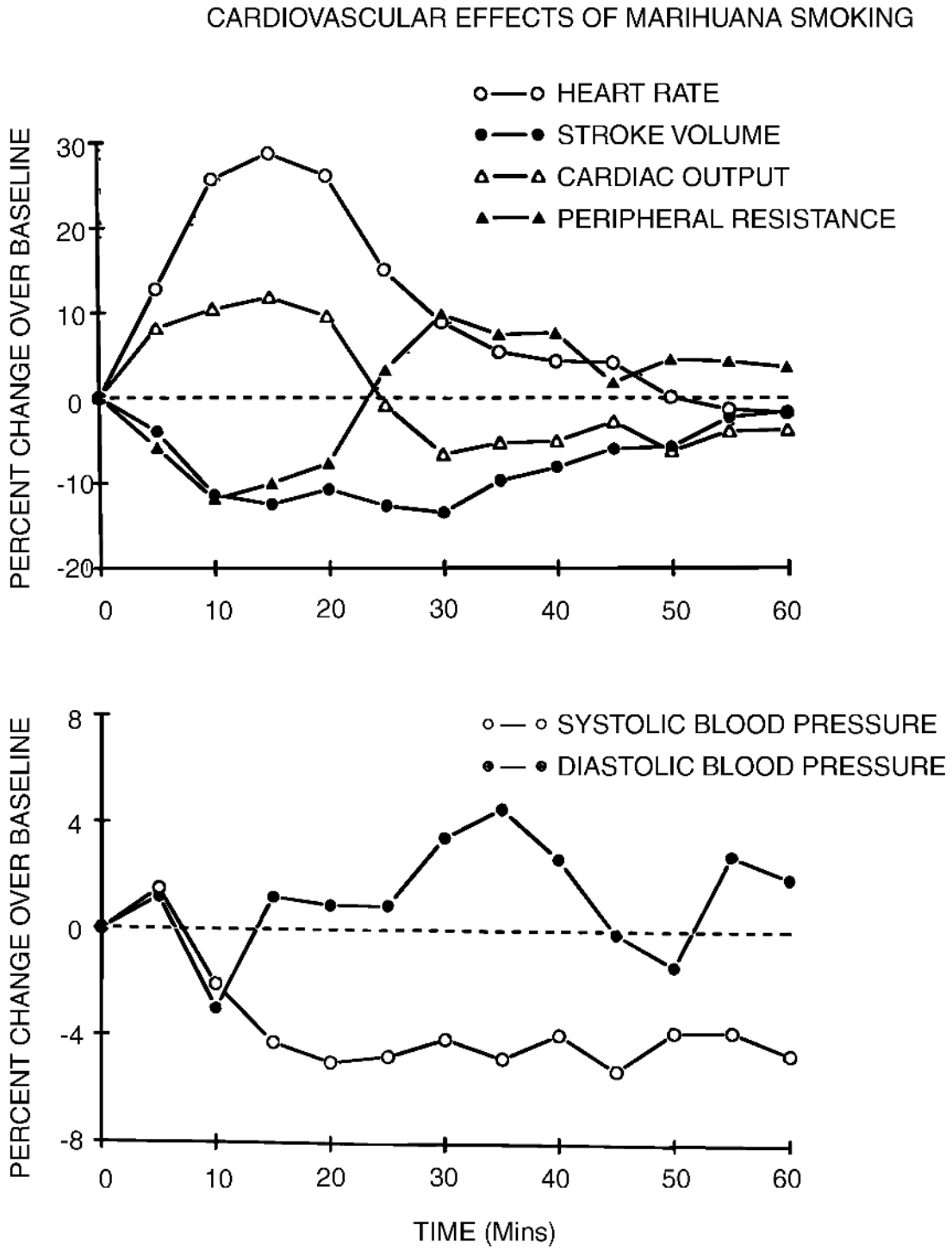
CHRONIC EFFECTS

A multitude of chronic effects on the immune system, and endocrine systems, respiratory tract (when inhaled), psyche, cognition, and psychomotor performance have been described.

Risks of Smoking

The greatest concern in connection with chronic effects of cannabis use does not pertain to the substance itself but its most common current route of application, inhalation by pipe or marijuana cigarette ("joint"), whereby combustion products that may damage the mucous membrane are inhaled (see Chapters 29 and 30). In the nineteenth century, in contrast, oral use was common both for medical and recreational use. For toxicological assess-

FIGURE 21.1. Cardiovascular Effects After Smoking a Marijuana Cigarette (2.8 Percent THC)



Source: Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and medicine.* Totowa, NJ: Humana Press, 1999, p. 248. Reprinted with permission.

ment it is important to differentiate between the endogenous plant compounds and their combustion products in cannabis smoke. Despite unsatisfying epidemiological data, evidence supports that damage similar to that associated with the use of tobacco occurs after cannabis smoking (see Chapter 29). Due to different causes (smoking without filter, longer duration of breath holding), one cannabis cigarette may correlate to about four tobacco cigarettes by the reckoning of some researchers. A heavy user of marijuana, smoking five joints per day, might therefore be at a similar risk to a smoker of one package of tobacco cigarettes per day.

Psyche and Cognition

Clear evidence exists which suggests that cannabis may precipitate latent schizophrenic psychosis in vulnerable individuals, but without increasing the incidence of the disease (see Chapter 27). Cannabis use may unfavorably influence the course of a schizophrenic psychosis. Whether and to what extent a number of psychiatric problems, such as depression, anxiety, indifference, withdrawal, etc., result from chronic cannabis intoxication is controversial. Some have questioned whether cannabis use is an accompanying symptom, or an attempt by the patient to solve this problem through self-treatment.

Neuropsychological studies have indicated that chronic heavy users may, depending on intensity and duration of use, show subtle impairments of memory, attention, and ability to organize and integrate complex information. The first large-scale longitudinal study in 1999 on the influence of marijuana use on decrease of cognitive performance did not find any such effect of cannabis.[24] However, the assessment instruments used have not been sufficiently sensitive to register slight impairments (see Chapter 27).

Tolerance and Dependency

Tolerance develops to the receptor-mediated effects of THC with continued usage. However, there are distinctions in their degree with different effects (see Chapter 5). Discontinuation of chronic THC use may cause rebound phenomena (transient increase in intraocular pressure, loss of appetite, etc.). Some chronic users report withdrawal symptoms after abrupt cessation. These symptoms, characterized by irritability, agitation, sleep disorder, hyperhidrosis, and loss of appetite, are generally mild. Cannabis dependency is less determined by physical than by psychological factors (see Chapters 20 and 23). Dependency and abuse potential of therapeutically employed Δ^9-THC is low (see Chapter 23).

In a German study of 1,458 current or previous cannabis users, 2 to 10 percent of the solely cannabis users were classified as substance dependent.[22] If those who also used other illegal drugs were included, 8 percent of

cannabis users were regarded as dependent, including 1 percent of the "occasional users," 7 percent of the "individual users," 10 percent of the "recreational users," and 28 percent of the "permanent users." Duration of consumption had no influence on the likelihood of the subject to quit use, an indication that the risk of dependency was independent of duration of use.

Immune System

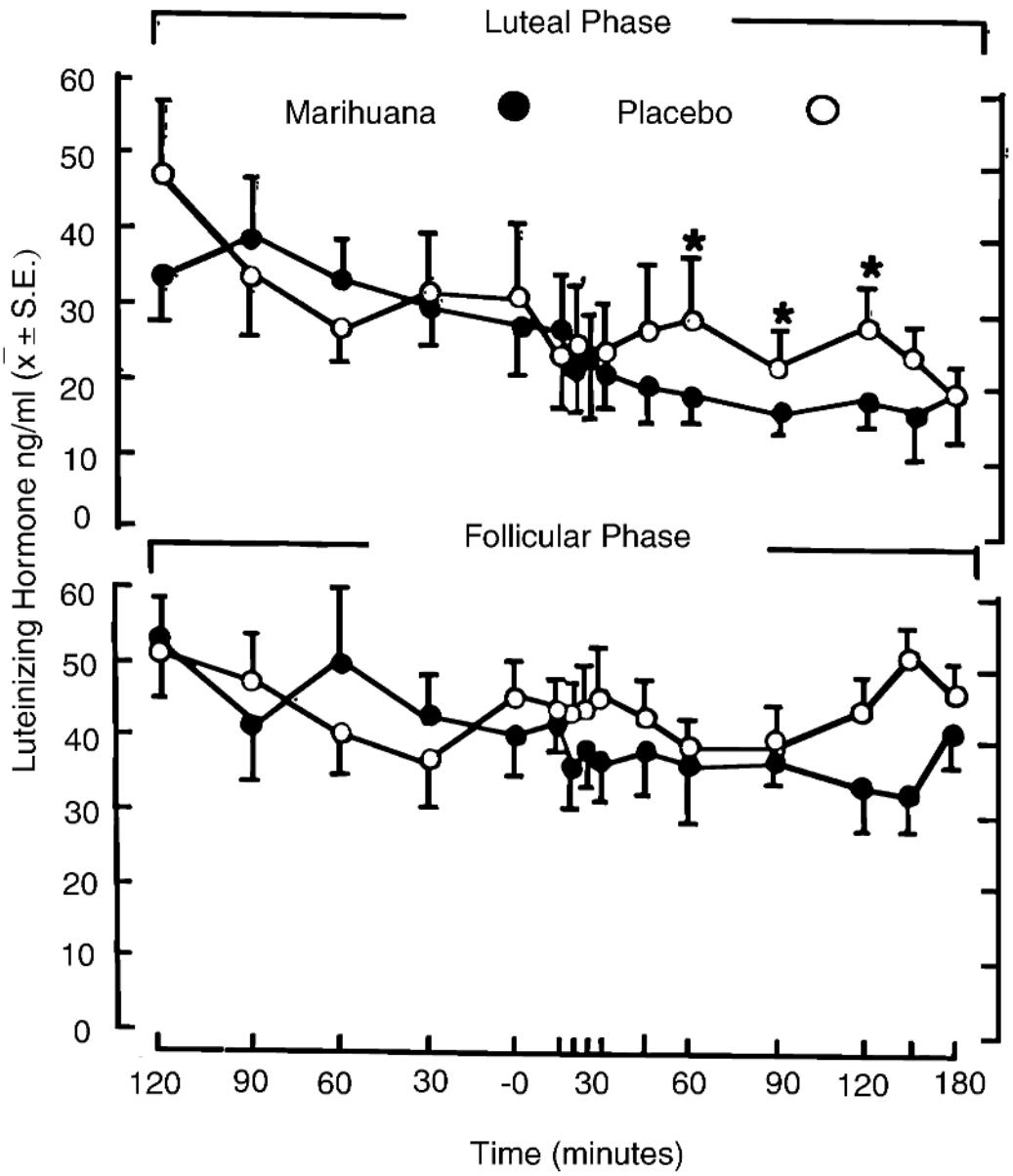
Cell and animal experiments have proven that THC exerts complex suppressive and stimulatory effects on humoral and cellular immunity (see Chapters 10 and 25). In human studies, conflicting results of cannabis usage on immunological parameters have been obtained. Even with heavy use, deleterious effects were weak, with questionable relevance for physical health. The World Health Organization summarized the effects of cannabinoids on the immune system as follows: "Many of their effects appear to be relatively small, totally reversible after removal of the cannabinoids, and produced only at concentrations or doses higher than those required for psychoactivity (more than 10 μM in vitro, or more than 5 mg/kg in vivo)" (p. 27).[32]

If THC was strongly immunosuppressive, severe consequences of cannabis use would be expected in the course of treatment in HIV, AIDS, and other infections, but this is not the case. However, even slight effects may be of clinical significance in immunocompromised individuals. The available data is inconsistent. In a prospective study of Kaslow et al.,[21] the use of cannabis in HIV infected persons was not associated with onset of AIDS. Di Franco et al.[7] did not observe any such influence of cannabis in HIV infected men in a six year epidemiological study. On the other hand, Tindall et al.[30] and Whitfield et al.[31] found evidence for such an association (see Chapter 25).

Hormonal System and Fertility

Cannabis and Δ^9-THC act on the hypothalamic-pituitary adrenal axis and in animal studies a multitude of endocrine processes are influenced by the drug affecting sexual and other hormones, including andrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and human growth hormone (HGH) as well as glucose metabolism[9] (see also Chapter 26). In some human studies modest disturbances of the menstrual cycle were noted in female cannabis users, while in others no disturbances were observed. Transient and generally mild effects on some hormones (prolactin, luteinizing hormone [LH]) have been observed in women after acute doses of THC, while others remained unaffected (follicle-stimulating hormone [FSH], progesterone, estrogen). The strongest effect has been described for LH in the luteal phase of the cycle, a transient significant decrease of plasma LH level (see Figure 21.2). In men, no consistent effects on hormonal parameters have been observed following acute application of

FIGURE 21.2. LH Levels Before and After (Zero Time) Smoking a Marijuana (•) or Placebo (o) Cigarette During the Luteal and Follicular Phases of the Menstrual Cycle



Source: Mendelson JH, Mello NK, Ellingboe J, Skupny AST, Lex BW, Griffin M. Marihuana smoking suppresses luteinizing hormone in women. *Journal of Pharmacology and Experimental Therapeutics* 1986;237(3):862-866. Reprinted with permission.

Note: In the luteal phase LH level showed a significant transient decrease ($p < 0.02$).

THC. Tolerance develops to hormonal effects even with high doses, such that chronic female and male cannabis users show normal hormone levels of all hormones.[9]

In animal studies, high THC doses caused a modest increase in abnormally formed sperm. Thus, the rate of sperm abnormalities in mice was 5.3 percent following five days of treatment with 10 mg/kg THC per day, 3.8 percent after treatment with 5 mg/kg THC, while the percentage of abnormalities in the controls was 1.5 percent.[33] After several weeks of daily smoking of eight to ten marijuana cigarettes a slight decrease in sperm count was observed in humans, without increasing the rate of morphological abnormalities or impairment of their function.[14]

Opposing views with regard to consequences of cannabis use on libido were evident even in writings of the antiquity.[1] Cohen notes in modern times: "The final paradox is that cannabis' employment for sexual arousal is predominantly an activity of young adults. The older age groups most in need of sexual support and assistance are less frequently involved in its use" (p. 55).[6]

Few epidemiological data on influences of cannabis on fertility exist, and these provide no definitive answers. In an Indian study, 150 married male cannabis users that initiated cannabis use shortly before marriage were compared to an equal number of opium users and nonusers of drugs. In the study, 1 percent of nonusers, 2 percent of cannabis users, and 10 percent of opium users were childless. Noteworthy in the study was the sterility rate in bhang users (cannabis leaves). With an average daily consumption of about 150 mg THC sterility was lower (0.4 percent) than in nonusers, whereas the users of ganja and charas (flowers and resin) with a daily consumption of about 300 mg THC sterility was clearly higher (5.7 percent).[5]

Mueller et al.[25] investigated effects of marijuana use on female sterility. There was a low increase of sterility risk in association with marijuana use—relative risk (RR), 1.7; 95 percent confidence interval (CI), 1.0-3.0. The risk was only increased in occasional users and not at all in more heavy users. Joesoef et al.[19] investigated the period of time from the desire to become pregnant until conception in 2,817 women. Regular users of cannabis became pregnant most quickly (mean 3.7 months). Tobacco smokers needed an average of 5.1 months, and drug-free women 4.3 months.

Other Hormones

In humans, oral application of therapeutic doses of THC does not increase plasma corticosterone or ACTH level. In contrast, smoking two marijuana cigarettes results in a transient significant increase in corticosterone concentration. Chronic heavy marijuana users do not show altered corticosterone or thyroid hormone levels. Cannabis use does not result in measurable changes in blood glucose level, but may influence glucose tolerance. However, relatively high doses are needed. Thus, 6 mg intravenously

applied THC influences glucose tolerance in some volunteers while others remain unaffected.[16] (1 mg THC iv = psychotropic threshold, see Table 21.1). (For a further review see the work of Grotenhermen[9] and Chapter 26).

Pregnancy

It is unlikely that cannabis causes embryonic or fetal malformations. Although epidemiological data on its effect on birth weight is inconsistent, there is evidence of subtle disturbances of cerebral development resulting in cognitive impairment in offspring of cannabis users (see Chapter 24). Some scientists assume such disturbances exist (see Chapter 24), while others believe that cannabis exerts no relevant negative effects.[8] Possibly, subtle cognitive marijuana-related disorders might not be observed before preschool or school age.

LEGAL CONSEQUENCES

Natural cannabis products are illegal in most countries. For the most part, no legal distinction is made between recreational and medical use.

If single cannabinoids (dronabinol, nabilone), that may be legally prescribed in some countries are not available, too expensive, or ineffective, therapeutic use of cannabis may provoke various repercussions for the patient who employs it. These include: criminal prosecution or fear thereof, paying a high price for an illegal drug, exposure to possible contamination (see Chapter 30), use of an unknown concentration of THC with possible variability in dosing, limited forms of administration, and even fear of discussion with the patient's family doctor. The illegality of cannabis presents various obstacles to clinical research.

EXTRAPOLATION OF ANIMAL DATA TO HUMANS

One advantage of animal studies is their thorough control of the conditions of THC administration, such as time, duration, and control of possible confounding factors. Therefore, they constitute an important element of toxicological research. However, for various reasons, caution is still required when using "data produced by those that continue to extrapolate animal data to humans without some attempt to discuss in detail the validity of their assumptions" (p. 117).[3]

There are different methods of extrapolation of animal data to humans. (For a discussion in connection with THC see the review by Grotenhermen[9]).

The first approach in comparing toxicological data from various animal species with that of man is based on *body weight*. Many biologic parameters such as water intake, creatinine clearance, and synthesis of hemoglobin can

TABLE 21.1. Order of Magnitude of THC Doses or THC Concentrations in Decimal Steps

Oral dose THC per kg body weight	Description (order of magnitude)	Maximal concentration in plasma or medium
0.1-0.2 mg/kg	placebo threshold, psychotropic threshold	3-5 ng/ml
1-2 mg/kg	heavy cannabis use	(15-30 ng/ml)
10-20 mg/kg	medium dose in animal study	100-150 ng/ml
100-200 mg/kg	high dose in animal study	(500-1,000 ng/ml)
–	medium cell-experimental dose	1 µg/ml
–	high cell-experimental dose	10 µg/ml

Source: Modified from Grotenhermen F. Pharmacological and toxicological basis of THC limits for food. In Grotenhermen F, Karus M, Lohmeyer D, eds. *Hemp Foods and THC Levels: A Scientific Assessment.* Sebastopol, CA: Hemptech, 1998.

be expressed as mathematical function of mass. However, many biological processes such as metabolic rate, cardiac function, and renal function are not directly proportional to body weight.

Another potential basis for the comparison of toxic effects between species is *body surface area*. For instance, the heat loss of warm-blooded animals is approximately proportional to its body surface. In studies on cancer drugs it was demonstrated that the maximum tolerated dose in different species (mouse, rat, dog, monkey, human) correlated quite well if adjusted to this parameter.[9] Bodies of small animals have a comparatively large surface to weight ratio. Thus, conversion factors are employed between different species.

If the specific toxicity of a compound is unknown, the best correlations can be achieved on the basis of *pharmacokinetic data,* such as absorption, distribution, metabolism, and excretion. Classical pharmacokinetic models are based on plasma concentration and AUC (area under the curve), such as plasma concentration over time, produced by known doses. Pharmacokinetics of Δ^9-THC in humans and in animals show some parallels and a number of conspicuous differences.[2,13]

Unfortunately, the results achieved by extrapolation on the basis of the models presented can be quite astonishing. One example is the lethal dose of THC (see the paragraph on overall toxicity). Instead of being 50 percent more sensitive, as was expected according to body surface, primates turned out to be at least five to ten times more resistant to THC.[29] It has not yet become quite clear how, at low doses, the relevant target parameters (effects on hormonal system, immune system, and fetus) would compare between species.

Examples of other chemical substances demonstrate a wide range of possible conversion factors. Alcohol, methyl mercury, and polychlorinated biphenyls cause embryonic malformations in humans. The toxic doses per kg body weight in animal studies ranged from 0.2 to 8.0 times the toxic dose observed in humans.[15]

Hence, animal data can provide an indication of the toxicity of THC in humans. However, reliable data on the toxicity of THC in humans are obtained only by observation of humans.

COMPARISON OF CANNABIS AND OTHER DRUGS

In the recent past, some studies have attempted to compare the health risks of the most common legal and illegal drugs. Two studies achieved special attention: a report by order of the French Health Ministry, the so-called "Roques-Report,"[26] and a study prepared for the World Health Organization.[11] Both reports concluded that heavy cannabis consumption causes less harm than heavy use of the most common other legal and illegal drugs (see Tables 21.2 and 21.3).

Hall et al.[11] point out that our scientific knowledge on the long-term effects of chronic cannabis use is preliminary. Compared to tobacco and alcohol, few epidemiological studies exist that give information on the chronic effects.

Use of all the investigated drugs could lead to dependency to a certain extent.[11] With one exception, the main health risks of cannabis use from the perspective of the solely cannabis smoker would be limited to daily users that consume the drug over a period of several years. These risks include the risk of a dependency syndrome, development of a chronic bronchitis, and involvement in motor vehicle accidents if the user drives under acute influence of the drug (see also Chapter 28). The latter could also affect occasional users.

TABLE 21.2. Comparison of the Hazards of Different Drugs

	Opiates	Cocaine	Alcohol	Benzo-diazepines	Cannabis	Tobacco
Physical dependency	*****	**	*****	***	**	****
Psychic dependency	*****	****	*****	****	**	*****
Nerve damage	**	****	****	–	–	–
Overall toxicity	**** (not in therapy)	****	****	*	*	***** (cancer)
Social hazards	*****	*****	****	**	**	–

Source: Modified from Roques B. *Problems posées par la dangerosité des drogues. Rapport du professeur Bernhard Roques au Secrétaire d'Etat à la Santé.* [A report to the French Ministry of Health]. Paris, 1998.

– = no effects, * = very weak effects, ** = weak effects, *** = moderate effects, **** = strong effects, ***** = very strong effects

TABLE 21.3. Comparison of Adverse Effects on Health for Heavy Users of the Most Harmful Common Form of Each Substance

	Marijuana	Alcohol	Tobacco	Heroin
Traffic and other accidents	*	**		*
Violence and suicide		**		
Overdose death		*		**
HIV and liver infections		*		**
Liver cirrhosis		**		
Heart disease		*	**	
Respiratory diseases	*		**	
Cancer	*	*	**	
Mental illness	*	**		
Dependency/addiction	**	**	**	**
Lasting effect on the fetus	*	**	*	*

Source: Hall W, Room R, Bondy S. Comparing the health and psychological risks of alcohol, cannabis, nicotine and opiate use. In: Kalant H, Corrigan W, Hall W, Smart R, eds. *The health effects of cannabis.* Toronto: Addiction Research Foundation, 1999, pp. 477-508.

* = less common or less well-established effect

** = important effect

REFERENCES

1. Abel EL. Marihuana and sex. A critical survey. *Drug and Alcohol Dependence* 1981;8(1):1-22.

2. Agurell S, Halldin M, Lindgren JE, Ohlsson A, Widman M, Gillespie H, Hollister L. Pharmacokinetics and metabolism of delta-1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacological Reviews* 1986; 38(1):21-43.

3. Campbell DB. Extrapolation from animals to man. The integration of pharmacokinetics and pharmacodynamics. *Annals of the New York Academy of Sciences* 1996;801:116-135.

4. Chan PC, Sills RC, Braun AG, Haseman JK, Bucher JR. Toxicity and carcinogenicity of delta 9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice. *Fundamental and Applied Toxicology* 1996;30(1):109-117.

5. Chopra GS, Jandu BS. Psychoclinical effects of long-term marijuana use in 275 Indian chronic users. A comparative assessment of effects in Indian and USA users. *Annals of the New York Academy of Sciences* 1976;282:95-108.

6. Cohen S. Cannabis and sex: Multifaceted paradoxes. *Journal of Psychoactive Drugs* 1982;14(1-2):55-58.

7. Di Franco MJ, Shephard HW, Hunter DJ, Tosteson TD, Ascher MS. The lack of association of marijuana and other recreational drugs with progression to AIDS in the San Francisco Men's Health Study. *Annals of Epidemiology* 1996;6(4):283-289.

8. Dreher MC, Nugent K, Hudgins R. Prenatal marijuana exposure and neonatal outcomes in Jamaica: An ethnographic study. *Pediatrics* 1994;93(2):254-260.

9. Grotenhermen F. Pharmacological and toxicological basis of THC limits for food. In Grotenhermen F, Karus M, Lohmeyer D, eds. *Hemp Foods and THC Levels: A scientific assessment*. Sebastopol, CA: Hemptech, 1998.

10. Hall W, Solowij N, Lemon J. *The health and psychological consequences of cannabis use*. Canberra: Commonwealth Department of Human Services and Health, Monograph Series No. 25, 1994.

11. Hall W, Room R, Bondy S. Comparing the health and psychological risks of alcohol, cannabis, nicotine and opiate use. In Kalant H, Corrigan W, Hall W, Smart R, eds. *The health effects of cannabis*. Toronto: Addiction Research Foundation, 1999, pp. 477-508.

12. Hänsel R. Cannabis. In von Bruchhausen F, ed. *Hagers Handbuch der pharmazeutischen Praxis*. Bd. 4, Drogen: A-D. Berlin/Heidelberg/New York: Springer, 1992.

13. Harvey DJ, Brown NK. Comparative in vitro metabolism of the cannabinoids. *Pharmacology, Biochemistry and Behavior* 1991;40(3):533-540.

14. Hembree WC, Nahas GG, Zeidenberg P, Huang HF. Changes in human spermatozoa associated with high dose marihuana smoking. *Advances in the Biosciences* 1978;22-23:429-439.

15. Hemminki K, Vineis P. Extrapolation of the evidence on teratogenicity of chemicals between humans and experimental animals: Chemicals other than drugs. *Teratogenesis, Carcinogenesis, and Mutagenesis* 1985; 5(4):251-318.

16. Hollister LE, Reaven GM. Delta-9-tetrahydrocannabinol and glucose tolerance. *Clinical Pharmacology and Therapeutics* 1974;16(2):297-302.

17. Hollister LE. Health aspects of cannabis. *Pharmacological Reviews* 1986; 38(1):1-20.

18. House of Lords Select Committee on Science and Technology. *Cannabis: The scientific and medical evidence*. London: The Stationery Office, 1998.

19. Joesoef MR, Beral V, Aral SO, Rolfs RT, Cramer DW. Fertility and use of cigarettes, alcohol, marijuana, and cocaine. *Annals of Epidemiology* 1993;3(1):592-594.

20. Joy JE, Watson SJ, Benson JA, eds. *Marijuana and medicine: Assessing the science base*. Washington, DC: Institute of Medicine, National Academy Press, 1999.

21. Kaslow RA, Blackwelder WC, Ostrow DG, Yerg D, Palenicek J, Coulson AH, Valdiserri RO. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals. A report from the Multicenter AIDS Cohort Study. *Journal of the American Medical Association* 1989;261(23):3424-3429.

22. Kleiber D, Soellner R, Tossmann P. *Cannabiskonsum in der Bundesrepublik Deutschland: Entwicklungstendenzen, Konsummuster und Einflußfaktoren*. Bonn: Bundesministerium für Gesundheit, 1997.

23. Koff WC. Marijuana and sexual activity. *Journal of Sex Research* 1974;10(3):194-204.

24. Lyketsos CG, Garrett E, Liang K-Y, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. *American Journal of Epidemiology* 1999;149(9):794-800.

25. Mueller BA, Daling JR, Weiss NS, Moore DE. Recreational drug use and the risk of primary infertility. *Epidemiology* 1990;1(3):195-200.

26. Roques B. *Problemes posées par la dangerosité des drogues. Rapport du professeur Bernhard Roques au Secrétaire d'Etat à la Santé*. [A report to the French Ministry of Health]. Paris, 1998.

27. Schnelle M, Grotenhermen F, Reif M, Gorter RW. Ergebnisse einer standardisierten Umfrage zur medizinischen Verwendung von Cannabisprodukten im deutschen Sprachraum [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. *Forschende Komplementärmedizin [Research in Complementary Medicine]* 1999;6(Suppl 3) 28-36.

28. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. *American Journal of Public Health* 1997;87(4):585-590.

29. Thompson GR, Rosenkrantz H, Schaeppi UH, Braude MC. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. *Toxicology and Applied Pharmacology* 1973;25(3):363-372.

30. Tindall B, Cooper DA, Donovan B, Barnes T, Philpot CR, Gold J, Penny R. The Sydney AIDS Project: Development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. *Australian and New Zealand Journal of Medicine* 1988;18(1):8-15.

31. Whitfield RM, Bechtel LM, Starich GH. The impact of ethanol and Marinol/marijuana usage on HIV+/AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, or dideoxyinosine therapy. *Alcoholism, Clinical and Experimental Research* 1997;21(1):122-127.

32. World Health Organization. *Cannabis: A health perspective and research agenda*. Geneva Division of Mental Health and Substance Abuse, WHO, 1997.

33. Zimmerman AM, Bruce WR, Zimmerman S. Effects of cannabinoids on sperm morphology. *Pharmacology* 1979;18(3):143-148.

Chapter 22

Acute Effects of Cannabis and the Cannabinoids

F. Markus Leweke

Acute effects of cannabinoids in both the central nervous and the peripheral organic systems depend on the dose as well as on the individual disposition of the consumer. Furthermore, the response varies with different pharmacokinetics such as the mode of administration (pulmonary or oral) and substance characteristics (Δ^9-THC, or a natural derivative in combination with other natural cannabinoids).

ACUTE EFFECTS ON THE CENTRAL NERVOUS SYSTEM

In animal studies, a large number of different species exhibited specific behavior following cannabis application.[9] Low doses of Δ^9-THC and other psychotropic cannabinoids led to a combination of sedative and stimulant effects, whereas higher doses had primarily sedative effects.[20] Furthermore, it has been shown that both Δ^9-THC and anandamide are sedative and analgesic. This has also been demonstrated on the spinal and brain stem level.[16,26] In addition, both substances reduced motor activity in rats.[36,37] Further effects of Δ^9-THC observed in animal studies include a reduction of body temperature, a decrease in reflex responses and in muscle tone, an impaired ability to carry out complex behavior and a decline in overt aggressive behavior,[15,40] the latter being especially prominent in primates.

In humans, the central nervous effects of Δ^9-THC were reported to vary with dosage, type of administration, the consumer's previous experiences with psychotropic drugs as well as with the consumer's individual vulnerability to the psychotropic action of Δ^9-THC.[33]

Consumer self-reports of acute clinical effects of cannabis in low and medium doses (2 to 10 mg Δ^9-THC) mostly pointed to qualitative changes in

sensory perception with a heightened external and internal sensitivity, especially with regard to visual stimuli, and to distortions of the subjective perception of time. Further effects during the acute time of action commonly reported are feelings of well-being, mild euphoria (a subjective high), relaxation and anxiolysis, and higher degrees of sedation.[3] However, the individual response to cannabinoids varies greatly between subjects;[17] a reason for this might be the selective action of and interaction between different natural cannabinoids, respectively.[24] Our own observations implicate that a dependence of Δ^9-THC effects on the situation of intake and the pre-experimental psychic condition of the consumer. Thus, the consumption of Δ^9-THC might increase an already tainted basic mood. Yet, at dosages of up to 5 mg Δ^9-THC, no significant differences in the psychotropic action were found in comparison to a placebo.[7]

Medium doses (10 to 20 mg Δ^9-THC) have been shown to lead to an intensification of emotional behavior and reactivity as well as to more prominent changes in perception and transient hallucinatory experiences.[20] But these effects usually are avoided by the common inhalation of cannabis wherein the fast bioavailability gives the consumer good individual command of these responses.

Thus, serious unwanted effects generally occur at high single doses of more than 20 mg Δ^9-THC, but due to the high inter-individual variability in the response to cannabis, these efforts might also be observed for lower doses in some cases. The most frequent unwanted psychic response is an acute panic reaction which occurs most often in inexperienced consumers or at high dosages of cannabis.[13] The most prominent sign of a panic reaction is the consumer's concern about losing control. Yet, this response remits spontaneously or can be quickly brought under control by "talking down." A sedative medication is normally not required, because the sedative effect of cannabis itself already contributes to the regulation of this reaction. In a small minority of cases, longer lasting or recurrent experiences of depersonalization have been observed. However, as for the more frequent panic reaction and because of their generally mild severity, experiences of depersonalization in acute cannabis intoxication rarely require further pharmacological intervention.[17]

Different assessments have been made regarding the frequency of acute paranoid reactions following cannabis consumption. Despite several reports of their occurrence even under experimental laboratory conditions, it is more likely that paranoid symptoms represent a reaction primarily moderated by characteristics of the environment and/or of the consumer's personality structure.[21]

Psychotic symptoms following acute cannabis consumption have been described. Their severity, duration, and frequency heavily depended on cultural and personality-related factors as well as on the frequency and inten-

sity of previous cannabis consumption.[4] Nevertheless, even a single intake of Δ^9-THC has been shown to release so-called short substance-induced psychotic disorders that mimic complex schizophreniform psychotic disorders. These psychotic states generally remit completely and quickly after the subsidence of the acute Δ^9-THC-effect, or after a couple of days. They are remembered completely by the affected person.[25,42] As a rule, the individual vulnerability to these psychotic states cannot be predicted for the medicinal use of psychotropic cannabinoids and consequently provides a special problem for the oral application of Δ^9-THC. Thus, according to present knowledge, the medicinal application of psychotropic cannabinoids to patients with an individual or genetic risk of schizophrenic or schizophreniform, bipolar affective or unipolar manic or maniform psychoses should be avoided whenever possible.

A toxic delirium due to cannabis has been observed only after ultra-high dosages. It becomes manifest by disturbances of memory function, orientation and consciousness.[29] Such a delirium has to be regarded as a nonspecific reaction that can be released by a variety of substances and whose origins cannot yet be conclusively explained. However, deliriant reactions to cannabis are self-limited and thus do not call for any special intervention.

The recurrent hypothesis alleging an increased propensity toward acts of violence under the acute influence of cannabis has not been empirically or experimentally supported to date. Studies on this topic have mainly pointed to a major role of pre-existing accentuated personality traits in the disinhibition of violent impulses during acute cannabis intoxication.[2]

The acute effects of cannabinoids on cognitive functions have frequently been studied under controlled laboratory conditions.[14,41] Regarding the findings of a variety of clinical effects of Δ^9-THC (see previous discussion), it is not surprising that these studies have been able to prove a large number of cognitive changes in the active phase of Δ^9-THC. Among these cognitive impairments are difficulties with concentration, disturbances of short-term memory, and loosening of associations that might impede goal-directed mental activities. For example, an increased error rate in simple visual or auditory tasks has been shown which suggests an inversely dose-related decrease of attention.[23,31,32] Furthermore, disturbances in fine motor control and coordination, and a psychomotor poverty as well as prolonged, but also unaffected reaction times have been reported to be among the possible consequences of Δ^9-THC-intake.[6,23] In addition, the clinically reported aberrations in visual perception[5,25] as well as in the subjective perception of time with an overestimation of the past time[19] have been replicated under experimental conditions. In summary, single, simple experimental designs have not been able to provide support for an assumed general impairment of cognitive functions but show complex response patterns caused by Δ^9-THC,

whereas a number of more complex experimental designs have demonstrated a significant effect of Δ^9-THC in nearly all studies.[41]

These cognitive effects of cannabinoids are reported to cause a deficiency in the ability to operate machinery or to drive a car. The latter is an especially controversial finding[35] (see also Chapter 28), but should nevertheless be considered when medical cannabinoids are employed.

It is noteworthy that a single intake of Δ^9-THC causes neither withdrawal syndromes nor the development of a substance-tolerance or addictive disorder.[12]

A further effect of Δ^9-THC and other cannabinoids agonists including anandamide is a marked increase of appetite which has been found in animal studies[44] and in studies on humans.[1] It has been suggested that the relaxant effects of cannabinoids on muscle tone shown in animals[15] are due to the central nervous effects of cannabinoids.[30]

EFFECTS OF CANNABINOIDS ON PERIPHERAL SYSTEMS

Cardiovascular Effects

It has been shown in animals that Δ^9-THC induces an antihypertensive action with concomitant bradycardia.[38] This effect varies by species.[9] Interestingly, anandamide exhibits significant antihypertensive effects in rats.[43]

In humans, cannabis regularly produces reversible and dose-dependent tachycardia and increased diastolic blood pressure (in lying position), which have been associated with a decreased parasympathetic tone.[8,18] At higher dosages, orthostatic hypotension may occur due to a dilation of blood vessels. This dilation of blood vessels seems to be the cause of conjunctival reddening that is commonly found after cannabis consumption. These effects may have their clinical expression in vertigo as well as in sudden syncope.

Interestingly, positron emission tomography in humans has shown that Δ^9-THC increases the regional blood flow in the frontal lobes, the insula, the gyrus cingulus, and subcortical areas with a right hemispheric focus. This increase in the right frontal blood flow has been shown to correlate with the clinical effects of Δ^9-THC.[27]

Pulmonary Effects

Regarding the pulmonary effects of cannabis, its form of administration has to be carefully considered. Following the smoking of natural cannabis, bronchial irritation and inflammatory changes have been observed in cannabis as well as in tobacco consumers (see Chapter 29). An acute effect of cannabis on the alveolar permeability could not be proven.[10] An increase of carboxyhemoglobin was found following the inhalation of cannabis smoke.[17]

Furthermore, Gong and colleagues[11] have shown that the oral application of Δ^9-THC and, though to a lesser degree, of Δ^8-THC (but not cannabidiol or cannabinol) have acute bronchodilatory effects. A development of a tolerance to Δ^9-THC was not observed despite its daily use.

Gastrointestinal Effects

In rodents, Δ^9-THC and, to a lesser degree, nabilone and cannabinol, reduce the intestinal motility and retard the intestinal passage.[39] These effects have been shown to be caused by a central CB_1-receptor-mediated mechanism.[22] In a recent study of these effects in humans, Δ^9-THC at a fixed dose of 10 mg/m^2 body surface (approximately equal to 240 µg/kg body weight) was also found to retard the gastrointestinal passage.[28]

Furthermore, Δ^9-THC has a cholinergic-mediated synergistic effect on the salivary gland, leading to hyposalivation and its accompanying mouth dryness.[17,34]

Ophthalmologic Effects

An acute effect of Δ^9-THC or cannabis after local or systemic application is the reduction of intraocular pressure (see Chapters 19 and 34). In addition, accommodation disturbances, a delayed light reaction of the pupils of the eyes, and a decrease in flow of tears might occur as an effect of Δ^9-THC.[17]

REFERENCES

1. Abel EL. Effects of marihuana on the solution of anagrams, memory and appetite. *Nature* 1971;231(5300):260-261.

2. Abel EL. The relationship between cannabis and violence: A review. *Psychological Bulletin* 1977;84(2):193-211.

3. Abood ME, Martin BR. Neurobiology of marijuana abuse. *Trends in Pharmacological Sciences* 1992;13(5):201-206.

4. Bron B. *Drogenabhängigkeit und Psychose*. Berlin; Heidelberg; New York: Springer-Verlag, 1982.

5. Carlin AS, Bakker CB, Halpern L, Post RD. Social facilitation of marijuana intoxication: Impact of social set and pharmacological activity. *Journal of Abnormal Psychology* 1972;80(2):132-140.

6. Chait LD, Pierri J. Some physical characteristics of NIDA marijuana cigarettes. *Addictive Behaviors* 1989;14(1):61-67.

7. Chesher GB, Bird KD, Jackson DM, Perrignon A, Starmer GA. The effects of orally administered delta 9-tetrahydrocannabinol in man on mood and performance measures: A dose-response study. *Pharmacology, Biochemistry and Behavior* 1990;35(4):861-864.

8. Clark SC, Greene C, Karr GW, Maccannell KL, Milstein SL. Cardiovascular effects of marihuana in man. *Canadian Journal of Physiology and Pharmacology* 1974;52(3):706-719.

9. Dewey WL. Cannabinoid pharmacology. *Pharmacological Reviews* 1986; 38(2):151-178.

10. Gil E, Chen B, Kleerup E, Webber M, Tashkin DP. Acute and chronic effects of marijuana smoking on pulmonary alveolar permeability. *Life Sciences* 1995; 56(23-24):2193-2199.

11. Gong H Jr, Tashkin DP, Simmons MS, Calvarese B, Shapiro BJ. Acute and subacute bronchial effects of oral cannabinoids. *Clinical Pharmacology and Therapeutics* 1984;35(1):26-32.

12. Grinspoon L, Bakalar JB. Marihuana. In Lowinson JH, Ruiz P, Millman RB, eds. JG Langrod, Baltimore: Williams Wilkins, 1997.

13. Halikas JA. Marijuana use and psychiatric illness. In Miller LL, eds. *Marijuana: Effects on human behavior*. New York: Academic Press, 1974.

14. Hall W, Solowij N. Adverse effects of cannabis. *Lancet* 1998;352(9740): 1611-1616.

15. Ham MT, De Jong Y. Absence of interaction between delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) in aggression, muscle control and body temperature experiments in mice. *Psychopharmacologia* 1975;41(2):169-174.

16. Hohmann AG, Martin WJ, Tsou K, Walker JM. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. *Life Sciences* 1995;56(23-24):2111-2118.

17. Hollister LE. Health aspects of cannabis. *Pharmacological Reviews* 1986; 38(1):1-20.

18. Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ. Characterization of the absorption phase of marijuana smoking. *Clinical Pharmacology and Therapeutics* 1992;52(1):31-41.

19. Jones RT, Stone GC. Psychological studies of marijuana and alcohol in man. *Psychopharmacologia* 1970;18(1):108-117.

20. Julien RM. *A primer of drug action*. New York: W. H. Freeman and Company, 1998.

21. Keeler MH, Moore E. Paranoid reactions while using marihuana. *Disorders of the Nervous System* 1974;35:535-536.

22. Krowicki ZK, Moerschbaecher JM, Winsauer PJ, Digavalli SV, Hornby PJ. Delta-9-tetrahydrocannabinol inhibits gastric motility in the rat through cannabinoid CB_1 receptors. *European Journal of Pharmacology* 1999;371(2-3):187-196.

23. Leweke FM, Kampmann C, Radwan M, Dietrich DE, Johannes S, Emrich HM, Münte TF. The effects of tetrahydrocannabinol on the recognition of emotionally charged words: An analysis using event-related brain potentials. *Neuropsychobiology* 1998;37(2):104-111.

24. Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich HM. Different effects of nabilone and cannabidiol on binocular depth inversion in man. *Pharmacology, Biochemistry and Behavior* 2000; 66(1):175-181.

25. Leweke FM, Schneider U, Thies M, Münte TF, Emrich HM. Effects of synthetic Δ^9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. *Psychopharmacology* 1999;142(3):230-235.

26. Martin WJ, Patrick SL, Coffin PO, Tsou K, Walker JM. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. *Life Sciences* 1995;56(23-24):2103-2109.

27. Mathew RJ, Wilson WH, Coleman RE, Turkington TG, DeGrado TR. Marijuana intoxication and brain activation in marijuana smokers. *Life Sciences* 1997; 60(23):2075-2089.

28. McCallum RW, Soykan I, Sridhar KR, Ricci DA, Lange RC, Plankey MW. Delta-9-tetrahydrocannabinol delays the gastric emptying of solid food in humans: A double-blind, randomized study. *Alimentary Pharmacology and Therapeutics* 1999;13(1):77-80.

29. Meyer ME. Psychiatric consequences of marihuana use: The state of the evidence. In Tinklenberg JR, ed. *Marijuana and health hazards: Methodologic issues in current research*. New York: Academic Press, 1975.

30. Miller AS, Walker JM. Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus. *European Journal of Pharmacology* 1996; 304(1-3):29-35.

31. Moskowitz H. Effects of marihuana on auditory signal detection. *Psychopharmacologia* 1974;40(2):137-145.

32. Moskowitz H, Sharma S, McGlothlin W. Effect of marihuana upon peripheral vision as a function of the information processing demands in central vision. *Perceptual and Motor Skills* 1972;35(3):875-882.

33. O'Brien CP. Drug Addiction and Drug Abuse. In Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gilman's The pharmacological basis of therapeutics*. New York: Macmillan, 1995.

34. Pertwee RG, Ross TM. Drugs which stimulate or facilitate central cholinergic transmission interact synergistically with delta-9-tetrahydrocannabinol to produce marked catalepsy in mice. *Neuropharmacology* 1991;30(1):67-71.

35. Robbe HWJ. *Influence of marijuana on driving*. Maastricht: Institute of Human Psychopharmacology, University of Limburg, 1994.

36. Romero J, Garcia L, Cebeira M, Zadrozny D, Fernandez-Ruiz JJ, Ramos JA. The endogenous cannabinoid receptor ligand, anandamide, inhibits the motor behavior: Role of nigrostriatal dopaminergic neurons. *Life Sciences* 1995;56(23-24): 2033-2040.

37. Romero J, Garcia-Palomero E, Lin SY, Ramos JA, Makriyannis A, Fernandez-Ruiz JJ. Extrapyramidal effects of methanandamide, an analog of anandamide, the endogenous CB_1 receptor ligand. *Life Sciences* 1996;58(15):1249-1257.

38. Seth R, Sinha S. Chemistry and pharmacology of cannabis. *Progress in Drug Research* 1991;36:71-115.

39. Shook JE, Burks TF. Psychoactive cannabinoids reduce gastrointestinal propulsion and motility in rodents. *Journal of Pharmacology and Experimental Therapeutics* 1989;249(2):444-449.

40. Sieber B. Influence of hashish extract on the social behaviour of encountering male baboons (Papio c. anubis). *Pharmacology, Biochemistry and Behavior* 1982; 17(2):209-216.

41. Solowij N. *Cannabis and cognitive functioning*. Cambridge: Cambridge University Press, 1998.

42. Thomas H. Psychiatric symptoms in cannabis users. *British Journal of Psychiatry* 1993;163:141-149.

43. Varga K, Lake K, Martin BR, Kunos G. Novel antagonist implicates the CB_1 cannabinoid receptor in the hypotensive action of anandamide. *European Journal of Pharmacology* 1995;278(3):279-283.

44. Williams CM, Kirkham TC. Anandamide induces overeating: mediation by central cannabinoid (CB_1) receptors. *Psychopharmacology* 1999;143(3):315-317.

Chapter 23

Cannabis and Dependence

Wendy Swift
Wayne Hall

TOLERANCE AND WITHDRAWAL

Tolerance

Tolerance occurs when a larger dose of a drug is required to achieve a given effect, or when a dose that normally achieves an effect is no longer sufficient to produce it. In a therapeutic context, tolerance may necessitate an increase in the dose required to achieve symptom relief. This may initially increase the risk of some unwanted side effects, although tolerance may also develop to these.

Tolerance to the biological effects of THC has been demonstrated in cultured cells and to many behavioral and physiological effects in humans and animal species.[2,13,21,28,30,32] The precise underlying mechanisms remain unknown, although they are believed to involve changes in cannabinoid receptor functioning.[2,11] Although the onset of tolerance is typically rapid, the rate of development depends on the effect and its duration is variable.[13,30] Tolerance is less definitive with intermittent exposure to THC.[2]

Jones and Benowitz studied the effects of a daily 210 mg dose of oral THC, administered in a fixed-dosing schedule to healthy male volunteers with an extensive history of cannabis use.[31] Over the 30-day study period, there was a decline in the positive effects of intoxication. A marked deterioration in social functioning in the early days of the high dose regimen almost completely reversed to baseline levels by study's end, while there was similar evidence of recovery in cognitive and psychomotor performance over the course of the study.

The magnitude of both the cardiovascular and subjective responses to smoking a single "joint" decreased with the length of time the subjects had

received a high dose of THC. After a few days of high dose THC, an increased heart rate was replaced by a normal, and in some cases a slowed, heart rate. Self-ratings of the "high" all but disappeared in the course of the study. Georgotas and Zeidenberg reported similar tolerance to the subjective effects of cannabis in humans.[21]

Withdrawal

Prior to the development of cannabinoid receptor antagonists, researchers precipitated withdrawal in animals that had been chronically maintained on THC by either abruptly ceasing THC administration or by administering the opioid antagonist naloxone. An abstinence or withdrawal syndrome was not consistently elicited, although many studies reported abstinence symptoms.[13,30,63] Kaymakcalan, for example, reported yawning, anorexia, piloerection, irritability, tremors, and photophobia in monkeys after abrupt cessation of a month-long schedule of high doses of THC.[34] In the few studies that assessed whether THC provided relief from cannabis withdrawal symptoms, it did not always do so.[2]

Early case reports of cannabis withdrawal in humans have been supported by reports of abstinence symptoms in laboratory settings.[13,30,63] Observational studies of clinical and nonclinical samples of long-term cannabis users have also frequently reported the occurrence of symptoms such as anxiety, insomnia, appetite disturbance, and depression.[41,47,51] In the absence of evidence that they were relieved by THC, it is difficult to confirm that these symptoms are part of a cannabis withdrawal syndrome.

Jones and Benowitz abruptly withdrew regular cannabis smokers after approximately two weeks on high doses of oral THC.[31] Within six hours, their subjects complained of "inner unrest," and after 12 hours "increased activity, irritability, insomnia, and restlessness were reported by the subjects and obvious to staff" (p. 632). The most common symptoms were " 'hot flashes', sweating, rhinorrhea, loose stools, hiccups and anorexia" (p. 632), which many subjects compared to a bout of influenza. Most important, the intensity of abstinence symptoms was positively correlated with THC dose and frequency of use, and symptoms were reduced by the resumption of cannabis use.[32] Georgotas and Zeidenberg reported similar symptoms during the first week of a four-week wash-out period in subjects who had received 210 mg THC in smoked cannabis a day for four weeks.[21] These effects disappeared during the final three weeks of the wash out.

Recent research with the antagonist SR 141716A confirmed that a withdrawal syndrome can be produced in rats, mice, and dogs that have been maintained on THC.[1,15,38,57] Caution is required in extrapolating animal data to humans, as dosing conditions may not be comparable. The compressed and accentuated symptoms produced by the antagonist may be much more dramatic than the milder and more prolonged symptoms occur-

ring under more naturalistic conditions of human use.[49] The relatively long half-life and complex metabolism of cannabis may also result in a less intense withdrawal syndrome than drugs such as opiates.[11]

Abuse Liability

Animals will not typically self-administer cannabis in the same way as they will opioids, cocaine, and alcohol, so there is no animal model of cannabis dependence. Recent evidence suggests that the cannabinoids may increase dopamine levels in the pathways presumed responsible for the reinforcing effects of opioids and cocaine.[14,54] However, the mechanisms underlying these effects and their implications for dependence liability in humans remain to be determined.[11]

A small body of research investigating the role of THC in human cannabis self-administration has provided suggestive evidence that THC plays a role in the reinforcing effects of cannabis.[6,26,35]

Anthony and Trinkoff [3] have argued that existing definitions of abuse liability overemphasize drug factors at the expense of others such as the environment (e.g., availability), which may override the inherent reinforcing properties of the drug. Recent twin[36] and proband studies[7] suggest that substance-specific and shared genetic and family/environmental influences may interact to make some individuals more vulnerable to dependence.

CANNABIS DEPENDENCE

Before 1964, the World Health Organization considered tolerance and withdrawal the markers of drug dependence.[64] In 1964, psychic (or psychological) dependence was considered the most powerful factor driving chronic intoxication.[17,65] However, for much of the 1960s and 1970s, the apparent absence of physical dependence supported the consensus view that cannabis was not a drug of dependence.[40]

A more liberal view of dependence, which reduced the previous emphasis on tolerance and withdrawal, emerged when Edwards and Gross's Alcohol Dependence Syndrome[19] was extended to other psychoactive drugs.[18] The Drug Dependence Syndrome described a clinically meaningful cluster of cognitive, behavioral, and physiological symptoms. These criteria were an awareness of a compulsion to use, a desire to stop despite continued use, relatively stereotyped drug taking (i.e., narrowing of repertoire), neuroadaptation (tolerance and withdrawal), withdrawal relief or avoidance, salience of drug use compared to other priorities, and rapid reinstatement after abstinence.

Epidemiological Evidence

The Epidemiologic Catchment Area (ECA) study provided the first epidemiological data on the population prevalence of DSM-III cannabis abuse and dependence in the United States in the early 1980s.[42] Cannabis was the most commonly used illicit drug, accounting for most of the cases of illicit drug abuse and/or dependence. Of the 6.2 percent of respondents who received a lifetime drug abuse and/or dependence diagnosis, 4.4 percent met criteria for cannabis abuse and/or dependence, followed by 1.7 percent for stimulants, 1.2 percent for sedatives, and 0.7 percent for opioid drugs. A third of those diagnosed with lifetime cannabis abuse/dependence (38 percent) reported active problems in the last year.

Among the 1,394 respondents who had used cannabis for at least two weeks on a daily basis, 17 percent felt dependent. Their most commonly reported symptoms were: requiring larger amounts (21 percent), having psychological (21 percent) or social (17 percent) problems attributed to cannabis, and inability to reduce use (8 percent). Few reported health problems (5 percent) or withdrawal sickness (3 percent).[3]

Similar estimates of the prevalence of cannabis dependence have been produced by population-based studies using similar methodologies to the ECA.[29,44,62]

The National Comorbidity Survey (NCS) conducted in the United States between 1990 and 1992[4] largely replicated the ECA findings. A lifetime DSM-III-R diagnosis of cannabis dependence was applicable to 4.2 percent of the sample. The proportion of lifetime cannabis users who met criteria for cannabis dependence was 9 percent, exceeded by nicotine (32 percent), heroin (23 percent), cocaine (17 percent), alcohol (15 percent), and stimulant (11 percent) dependence.

The Australian National Survey of Mental Health and Well-Being[25] found cannabis accounted for more dependence disorders than any other illicit drug, with 1.7 percent of adults qualifying for a dependence diagnosis, and 0.1 percent meeting harmful use criteria in the previous year. One in four (23 percent) of those who had used cannabis more than five times in the last year met ICD-10 criteria for cannabis dependence or harmful use in that year.

Studies of Long-Term Users

A small amount of literature exists on nonclinical populations of long-term cannabis users in naturalistic settings. Early studies conducted in Egypt,[45] India,[12] Germany,[55] Greece,[46] Costa Rica,[10] and Jamaica[43] provided inconsistent evidence for cannabis dependence among long-term users. Symptoms such as stereotyped use patterns, persistent desire to quit, tolerance, chronic intoxication, mild withdrawal and continued use despite

problems were reported in the Egyptian, Indian, and German studies. There were inconsistent reports of withdrawal symptoms in the Costa Rican, Jamaican, and Greek studies. Dependence was not the main focus of this research, so there was often little systematic investigation of phenomena other than withdrawal, which was then considered a defining symptom of dependence.

Kandel and Davies described problems reported by a subset of daily cannabis users (ages 28 to 29 years) who were recruited in a large prospective study (n = 1,222) of the consequences of adolescent drug use.[33] The major adverse consequences of cannabis use among those who had ever experienced a near-daily period of use were subjectively experienced cognitive deficits, reduced energy, depression, and, for males, problems with their spouses.

Recent Australian research identified a substantial proportion of long-term cannabis users as dependent. An examination of 243 rural long-term users, who had been consuming cannabis several times weekly for an average of 19 years, found that 57 percent qualified for both a lifetime DSM-III-R and a last year ICD-10 cannabis dependence diagnosis.[53] The most commonly reported DSM-III-R dependence criterion was frequent intoxication during daily activities (73 percent), while a strong urge to use was the most commonly endorsed ICD-10 symptom (75 percent). Few reported experiencing withdrawal symptoms (5 percent) or engaging in withdrawal relief (20 percent) but half (54 percent) reported the development of tolerance. Only a minority (26 percent) of these users believed they had a problem with cannabis. They were generally positive in their overall evaluation of their use and very few (9 percent) had sought professional help to cut down or stop.

A study of 200 long-term cannabis users in Sydney, who had used cannabis at least weekly for a mean of 11 years, found that 92 percent met lifetime criteria for a DSM-III-R dependence diagnosis and 40 percent were diagnosed as severely cannabis dependent.[50,51] Syndrome onset occurred within one year of commencing weekly use. Tolerance (78 percent) and withdrawal (76 percent) were very common but withdrawal relief was not as frequently reported (39 percent). Approximately three-quarters also met criteria for cannabis dependence within the past year according to DSM-III-R (77 percent) and ICD-10 (72 percent) criteria. A follow-up of this group found that cannabis use patterns and dependence symptoms were relatively stable over a year.[52] The majority (81 percent) of the follow-up sample met criteria for a dependence diagnosis during the previous year on at least one of three dependence measures. There was marginally more "remission" of dependence than new cases of cannabis dependence.

Clinical Populations

There is a small but consistent demand for professional help with cannabis-related problems in Australia, the United States, and Europe. The National Census of Clients of Australian Treatment Service Agencies[56,61] found that the proportion of cases for which cannabis was the *main* drug problem increased from 4 percent in 1990 to 7 percent in 1995. Between 1994 and 1998 cannabis was the primary drug of abuse for between 11 percent and 26 percent of clients of treatment agencies in the United States. These clients were predominantly male, polydrug users with no previous treatment experience, and a third were under 20 years of age.[59,60]

Cannabis was the primary drug problem for between 2 and 16 percent of clients attending treatment agencies in the European Union in 1998.[20] The Jellinek Centre in Amsterdam was seeing three to four cannabis-smoking clients a week in late 1996,[37] and a minimal intervention aimed at developing self-control strategies was provided to heavy smokers aged 15 to 25 years.[16] A Swedish program[58] reported that its clients typically complained of symptoms such as: unsuccessful attempts to stop or moderate use and frequent (often daily) intoxication, despite suffering adverse effects which they recognized were connected with their cannabis use. These included sleeplessness, depression, diminished ability to concentrate and memorize, and blunting of emotions.

Stephens and colleagues recruited 382 people into a controlled trial of two types of cannabis-specific treatment over three months.[48] Their clients reported the following adverse consequences of cannabis use in the 90 days before assessment: inability to stop using (93 percent), feeling bad about abusing cannabis (87 percent), procrastinating (86 percent), loss of self-confidence (76 percent), memory loss (67 percent), and withdrawal symptoms (51 percent). Symptoms related to the salience and the compulsive nature of their cannabis use were most common. Similar data have been reported from recent U.S.[8,47] and Australian treatment trials of interventions for cannabis use.[41] In the Australian study, 95 percent of 180 long-term cannabis users recruited to participate met criteria for cannabis dependence on three diagnostic instruments. Withdrawal/withdrawal relief was ranked as the most prevalent DSM-IV criterion (97 percent), suggesting its salience to this group and its potential role in prompting help seeking.

TOLERANCE, DEPENDENCE, AND THERAPEUTIC CANNABINOID USE

It is uncertain how relevant the existing research on dependence to THC and cannabis is to the therapeutic use of different forms of cannabinoids. Although tolerance may develop readily to quite low doses of THC in ani-

mals, humans seem to need more sustained exposure to high doses.[13] There is no reliable human data on the doses or duration of dosing that are required to develop other dependence symptoms. On the basis of the epidemiological literature, the risk of developing dependence among those who have ever tried cannabis has been estimated at about 1 chance in 10, with the risk increased to about 1 in 5 to 1 in 3 among more regular users.[24] It is uncertain whether the risk of dependence in regular recreational users can be applied to patients using cannabinoids for therapeutic reasons. A review of several indicators of the abuse potential of dronabinol found little evidence of such a problem.[9] This is clearly a research priority for therapeutic cannabinoid use, the results of which may well improve our limited understanding of the risks and consequences of cannabis dependence.

Until further research is undertaken only the following generalizations can be made. First, the risks of marked tolerance, withdrawal symptoms, and dependence are probably low when THC is given for a limited period as a short course of treatment, such as, to reduce nausea and vomiting during cancer chemotherapy or radiotherapy. Given the benefits of increasing compliance with therapy for potentially life-threatening illness (e.g., cancer chemotherapy), these risks will probably be judged to be well worth taking.

Second, the risks of tolerance and dependence to cannabinoids are less certain when they are used to treat symptoms of chronic diseases, such as glaucoma, multiple sclerosis, and neurological disorders. Tolerance may be more of an issue in these circumstances, although some reports indicate that patients achieve stabilization of dose and persistence of therapeutic benefit.[5,22,39] Other symptoms of dependence may be more likely in these cases (e.g., see the work of Holdcroft and colleagues[27] for possible indications of withdrawal during treatment with oral THC). Even if the risks of dependence are as high as those reported in daily recreational users, they may be judged to be worth bearing for relief from the distressing symptoms of chronic illnesses that disable and markedly interfere with the person's quality of life. In the case of terminal illnesses, such as cancer and AIDS, the therapeutic aim may be to decrease the short-term adverse consequences of a fatal condition. In these cases the risk of dependence will be low on the list of concerns.[23]

The major clinical issue in the chronic therapeutic use of cannabinoids is informed patient consent. For patients to give informed consent they would need to know about the risks of dependence so that they could weigh it among the short- and long-term adverse effects and benefits of therapeutic cannabinoid use. Patients would need to be told about the type of dependence symptoms that they may experience, the possible side effects of daily cannabinoid use (e.g., on memory and concentration), the severity of withdrawal symptoms they may experience if they choose to stop, and where to seek assistance if it was required.

REFERENCES

1. Aceto MD, Scates SM, Lowe JA, Martin BR. Dependence studies on Δ^9-tetrahydrocannabinol: Studies on precipitated and abrupt withdrawal. *Journal of Pharmacology and Experimental Therapeutics* 1996;278(3):1290-1295.

2. Adams IB, Martin BR. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 1996;91(11):1585-1614.

3. Anthony JC, Trinkoff AM. United States epidemiological data on drug use and abuse: How are they relevant to testing abuse liability on drugs? In Fischman MW, Mello NK, eds. *Testing for abuse liability of drugs in humans* (Research Monograph No. 92). Rockville, MD: National Institute on Drug Abuse, 1989, pp. 241-266.

4. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 1994;2:244-268.

5. Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangeo B, Morales JO, Murphy R, Powderly W, Plasse TF, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 1997;14(1):7-14.

6. Beardsley PM, Kelly TH. Acute effects of cannabis on human behavior and central nervous system functions. In Kalant H, Corrigall W, Hall W, Smart R, eds. *The health effects of cannabis*. Toronto, Canada: Centre for Addiction and Mental Health, 1999, pp. 129-169.

7. Bierut LJ, Dinwiddie SH, Begleiter H, Crowe RR, Hesselbrock V, Nurnberger JI, Porjesz B, Schuckit MA, Reich T. Familial transmission of substance dependence: Alcohol, marijuana, cocaine, and habitual smoking. A report from the Collaborative Study on the Genetics of Alcoholism. *Archives of General Psychiatry* 1998;55(11):982-988.

8. Budney AJ, Radonovich KJ, Higgins ST, Wong C. Adults seeking treatment for marijuana dependence: A comparison to cocaine-dependent treatment-seekers. *Experimental and Clinical Psychopharmacology* 1998;6(4):419-426.

9. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). *Journal of Psychoactive Drugs* 1998;30(2):187-196.

10. Carter WE, Coggins W, Doughty PL. *Cannabis in Costa Rica: A study of chronic marijuana use*. Philadelphia, PA: Institute for the Study of Human Issues, 1980.

11. Childers SR, Breivogel CS. Cannabis and endogenous cannabinoid systems. *Drug and Alcohol Dependence* 1998;51(1-2):173-187.

12. Chopra GS, Jandu BS. Psychoclinical effects of long-term marijuana use in 275 Indian chronic users. A comparative assessment of effects in Indian and USA users. *Annals of the New York Academy of Sciences* 1976;282:95-108.

13. Compton D, Dewey W, Martin B. Cannabis dependence and tolerance production. *Advances in Alcohol and Substance Abuse* 1990;9(1-2):129-147.

14. Compton DR, Harris LS, Lichtman AH, Martin BR. Marihuana. In Schuster CR, Kuhar MJ, eds. *Pharmacological aspects of drug dependence: Toward an integrated neurobehavioral approach*. Berlin, Germany: Springer, 1996, pp. 83-158.

15. Cook SA, Lowe JA, Martin BR. CB_1 receptor antagonist precipitates withdrawal in mice exposed to Δ^9-tetrahydrocannbinol. *Journal of Pharmacology and Experimental Therapeutics*, 1998;285(3):1150-1156.

16. Dupont H, Niewijk A. Self-control training for young smokers: Cannabis project. *Jellinek Quarterly,* 1996;3:11.

17. Eddy NB, Halbach H, Isbell H, Seevers MH. Drug dependence: Its significance and characteristics. *Bulletin of the World Health Organization* 1965;32(5): 721-733.

18. Edwards G, Arif A, Hodgson R. Nomenclature and classification of drug-and alcohol-related problems: A WHO memorandum. *Bulletin of the World Health Organization* 1981;59(2):225-242.

19. Edwards G, Gross MM. Alcohol dependence: Provisional description of a clinical syndrome. *British Medical Journal* 1976;1(6017):1058-1061.

20. European Monitoring Centre for Drugs and Drug Addiction. *1998 Annual report on the state of the drugs problem in the European Union: Summary and highlights*. Luxembourg: Office for Official Publications of the European Communities. Retrieved April 27, 1999 from the World Wide Web: <http://www.emcdda.org/assets/multimedia/Hilite_98_EN.pdf>.

21. Georgotas A, Zeidenberg P. Observations on the effects of four weeks of heavy marijuana smoking on group interaction and individual behavior. *Comprehensive Psychiatry* 1979;20(5):427-432.

22. Grinspoon L, Bakalar JB. *Marijuana: Forbidden medicine*. New Haven, CT: Yale University Press, 1993.

23. Gurley RJ, Aranow R, Katz M. Medical marijuana: A comprehensive review. *Journal of Psychoactive Drugs* 1998;30(2):137-147.

24. Hall W, Solowij N, Lemon J. *The health and psychological consequences of cannabis use* (National Drug Strategy Monograph Series No.25). Canberra, Australia: Australian Government Publishing Service, 1994.

25. Hall W, Teesson M, Lynskey M, Degenhardt L. The 12-month prevalence in the past year of substance use and ICD-10 substance use disorders in Australian adults: Findings from the National Survey of Mental Health and Well-Being. *Addiction* 1999;94(10):1541-1550.

26. Haney M, Comer SD, Ward AS, Foltin RW, Fischman MW. Factors influencing marijuana self-administration by humans. *Behavioural Pharmacology* 1997;8(2-3):101-112.

27. Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 1997;52(5):483-486.

28. Hollister LE. Health aspects of cannabis. *Pharmacological Reviews* 1986; 38(1):1-20.

29. Hwu HG, Compton WM. Comparison of major epidemiological surveys using the diagnostic interview schedule. *International Review of Psychiatry* 1994; 6:309-327.

30. Jones RT. Cannabis tolerance and dependence. In Fehr KO, Kalant H, eds. *Cannabis and health hazards: Proceedings of an ARF/WHO scientific meeting on adverse health and behavioral consequences of cannabis use*. Toronto, Canada: Addiction Research Foundation, 1983, pp. 617-689.

31. Jones RT, Benowitz N. The 30-day trip—Clinical studies of cannabis tolerance and dependence. In Braude MC, Szara S, eds. *Pharmacology of marijuana* (Volume 2). New York: Academic Press, 1976, pp. 627-642.

32. Jones RT, Benowitz N, Herning RI. The clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 1981;21(8-9 suppl):143S-152S.

33. Kandel DB, Davies M. Progression to regular marijuana involvement: Phenomenology and risk factors for near daily use. In Glantz M, Pickens R, eds. *Vulnerability to drug abuse*. Washington, DC: American Psychological Association, 1992, pp. 211-253.

34. Kaymakcalan S. Physiological and psychological dependence on THC in rhesus monkeys. In Paton WDM, Crown J, eds. *Cannabis and its derivatives*. London: Oxford University Press, 1972, pp. 142-147.

35. Kelly TH, Foltin RW, Emurian CS, Fischman MW. Effects of Δ^9-THC on marijuana smoking, dose choice, and verbal report of drug liking. *Journal of the Experimental Analysis of Behavior* 1994;61(2):203-211.

36. Kendler KS, Prescott CA. Cannabis use, abuse, and dependence in a population-based sample of female twins. *American Journal of Psychiatry* 1998; 155(8):1016-1022.

37. Kerssemakers R. Treatment of hashish addicts: Hashish problem still too often underestimated. *Jellinek Quarterly* 1996;3:4-5.

38. Lichtman AH, Wiley JL, LaVechhia KL, Neviaser ST, Arthur DB, Wilson DM, Martin BR. Effects of SR 141716A after acute and chronic cannabinoid administration in dogs. *European Journal of Pharmacology* 1998;357(2-3):139-148.

39. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *European Archives of Psychiatry and Neurological Sciences* 1990;240(1):1-4.

40. National Commission on Marihuana and Drug Abuse. *Marihuana: A signal of misunderstanding. First report*. Washington, DC: U.S. Government Printing Office, 1972.

41. Rees V, Copeland J, Swift W. Brief cognitive behavioural interventions for cannabis dependence. In Dillon P, Topp L, Swift W, eds. *Illicit drugs: Current issues and responses. Proceedings from the Eleventh National Drug and Alcohol Re-*

search Centre Annual Symposium (Monograph No. 37). Sydney: National Drug and Alcohol Research Centre, 1998, pp. 111-124.

42. Robins LN, Regier DA, eds. *Psychiatric disorders in America: The epidemiologic catchment area study.* New York: Free Press, 1991.

43. Rubin V, Comitas L. *Ganja in Jamaica: A medical anthropological study of chronic marijuana use.* The Hague, The Netherlands: Mouton Publishers, 1975.

44. Russell JM, Newman SC, Bland RC. Drug abuse and dependence. *Acta Psychiatrica Scandinavica* 1994;376 (Suppl):54S-62S.

45. Soueif MI. Hashish consumption in Egypt, with special reference to psychosocial aspects. *Bulletin on Narcotics* 1967;19:1-11.

46. Stefanis C, Dornbush R, Fink M, eds. *Hashish: Studies of long-term use.* New York: Raven Press, 1977.

47. Stephens RS, Roffman RA. Extended versus brief treatment for marijuana use. *Journal of Consulting and Clinical Psychology* 2000;68(5):898-908.

48. Stephens RS, Roffman RA, Simpson EE. Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology* 1993;61(6):1100-1104.

49. Swan N. Marijuana antagonist reveals evidence of THC dependence in rats. *NIDA Notes* 1995;10:1-6.

50. Swift W, Copeland J, Hall W. Choosing a diagnostic cut-off for cannabis dependence. *Addiction* 1998;93(11):1681-1692.

51. Swift W, Hall W, Copeland J. *Cannabis dependence among long-term users in Sydney, Australia* (Technical Report 47). Sydney: National Drug and Alcohol Research Centre, 1997.

52. Swift W, Hall W, Copeland J. One year follow-up of cannabis dependence among long-term cannabis users in Sydney, Australia. *Drug and Alcohol Dependence* 2000;59(3):309-318.

53. Swift W, Hall W, Didcott P, Reilly D. Patterns and correlates of cannabis dependence among long-term users in an Australian rural area. *Addiction* 1998; 93(8):1149-1160.

54. Tanda G, Pontieri FE, di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. *Science* 1997;276(5327):2048-2050.

55. Tennant FS, Groesbeck CJ. Psychiatric effects of hashish. *Archives of General Psychiatry* 1972;27(1):133-136.

56. Torres ML, Mattick RP, Chen R, Baillie A. *Clients of treatment service agencies: March 1995 Census findings.* Canberra, Australia: Commonwealth Department of Human Services and Health, 1995.

57. Tsou DT, Patrick SL, Walder JM. Physical withdrawal in rats tolerant to Δ^9-tetrahydocannabinol precipitated by a cannabinoid receptor antagonist. *European Journal of Pharmacology* 1995;280(3):R13-R15.

58. Tunving K, Lundquist T, Erikkson D. "A way out of the fog": An outpatient program for cannabis users. In Chesher G, Consroe P, Musty R, eds. *Marijuana: An*

international research report. Canberra, Australia: Australian Government Publishing Service, 1988, pp. 207-212.

59. United States Office of National Drug Control Policy. *Pulse check: National trends in drug abuse. December 1994*. Washington, DC: Office of National Drug Control Policy, 1994.

60. United States Office of National Drug Control Policy. Pulse check: National trends in drug abuse. Winter 1998. Washington, DC: Office of National Drug Control Policy. Retrieved April 27, 1999 from the World Wide Web: <http://www.whitehousedrugpolicy.gov/drugfact/pulsechk/winter98/conents.html>.

61. Webster P, Mattick RP, Baillie A. Characteristics of clients receiving treatment in Australian drug and alcohol agencies: A national census. *Drug and Alcohol Review* 1992;11:111-119.

62. Wells JE, Bushnell JA, Joyce PR, Oakley-Browne MA, Hornblow AR. Problems with alcohol, drugs and gambling in Christchurch, New Zealand. In Abbot M, Evans K, eds. Alcohol and drug dependence and disorders of impulse control. Auckland, New Zealand: Alcohol Liquor Advisory Council, 1992, pp. 3-13.

63. Wikler A. Aspects of tolerance to and dependence on cannabis. *Annals of the New York Academy of Sciences* 1976;282:126-147.

64. World Health Organization Expert Committee on Addiction Producing Drugs. Seventh report (Technical Report Series). Geneva, Switzerland: World Health Organization, 1957.

65. World Health Organization Expert Committee on Addiction Producing Drugs. Thirteenth report (Technical Report Series). Geneva, Switzerland: World Health Organization, 1964.

Chapter 24

Pregnancy

Peter A. Fried

There is an unfortunate and surprising dearth of information pertaining to the consequences of marijuana use during pregnancy, particularly with respect to the long-term consequences upon the offspring. It is unfortunate because, from a policy point of view, there are no lack of individuals willing to state strong (very often subjective) opinions about the effects or lack of effects of marijuana upon the unborn child. This is surprising in that cannabis is the most commonly used illicit drug among women of childbearing age.

In NIDA's (National Institute on Drug Abuse) most recently completed the Pregnancy and Health Survey based on 1992 information, self-reported marijuana use during pregnancy was 2.9 percent.[36] This figure is considerably below that reported in a number of longitudinal, prospective cohort studies investigating cannabis use and pregnancy with rates of use ranging from 10 to 16 percent in middle-class samples[22,29,32] to 23 to 30 percent in inner-city populations.[10,42,45]

The putative consequences of cannabis use during pregnancy can be examined from a number of perspectives including the drug's effect upon the course of pregnancy, morphology, growth, and developmental course of behavior from the newborn period onward. Because much of the available data, particularly in offspring older than three, arises from an ongoing, longitudinal Canadian study, the protocol of this work will be briefly summarized.

Since 1978, an ongoing longitudinal study, the Ottawa Prenatal Prospective Study (OPPS), has been investigating the effects of marijuana and cigarettes inhaled during pregnancy. Mothers-to-be were informed of the study by their obstetricians or by notices in waiting rooms or prenatal clinics in the four largest Ottawa hospitals. The sample is representative of the English-

Research arising from the OPPS was supported by grants from NIDA.

speaking Ottawa population.[22] Upon volunteering, each subject was interviewed once during each of the trimesters remaining in her pregnancy. Birth data have been collected from 682 women in the Ottawa area.[22] For pragmatic reasons approximately 180 offspring were chosen to be followed beyond the neonatal period.

During each of the pregnancy interviews, information was collected concerning sociodemographic status, mother's health (both current and prior to the pregnancy), father's health history, previous obstetrical history, a 24-hour dietary recall, and past and present drug use with particular emphasis upon cannabis, cigarettes, and alcohol. For the drug histories, information was gathered pertaining to the year before pregnancy and each trimester of pregnancy.

IMPACT ON THE COURSE OF PREGNANCY

Fried et al.[26] found a statistically significant reduction of approximately one week in the gestational age of infants born to mothers who used marijuana six or more times per week. Over the centuries, in many parts of the world, cannabis has been reported to hasten childbirth, with observers noting that the drug increases the frequency and intensity of contractions.[1] A report by Greenland et al.[30] that precipitate labor was significantly more frequent among women who reported using marijuana is consistent with the folk medicine and may be related to the shortened gestation noted in the OPPS sample. The approximate one week reduction in gestation length observed is of questionable clinical significance in and of itself. However, as the effect was dose related, the shortened gestation length may take on clinical significance if large amounts of the drug are consumed and/or if lifestyle habits include other risk factors such as alcohol. Other researchers,[27,32] but not all,[42,10] have reported an association between marijuana use during pregnancy and preterm delivery.

In the OPPS, no association with cannabis use and subjects' miscarriage rates, types of presentation at birth, Apgar status, and the frequency of complications or major physical abnormalities at birth were found.[11,14] No patterns of minor physical anomalies were noted among the offspring of marijuana users although two anomalies, true ocular hypertelorism and severe epicanthus, were observed only among children of heavy users of cannabis.[37] In general, researchers have not reported an association between prenatal cannabis use and morphologic abnormalities in offspring[10] and, as reviewed elsewhere,[6,37] the few reports of increased physical abnormalities may reflect a lack of control for confounding factors and/or the relative risk status of the women in the study.

The lifestyle and concomitant risk status is an important issue in interpreting prenatal marijuana outcomes. For example, in the low-risk sample

of the OPPS, no evidence of increased meconium staining was noted among the newborns of the heavy marijuana users.[14] This observation contrasts with the first but not second of two reports by Greenland and associates.[29,30] One of the primary differences between the two Greenland studies was the generally higher standard of living and health among the sample in the later[29] report. These subjects were quite similar, demographically, to the OPPS sample. A study utilizing pregnant rats[5] bears directly upon the critical role that lifestyle may have in interacting with the teratogenic effects of cannabis. Briefly, different groups of pregnant rats were exposed to marijuana smoke while receiving diets varying in protein content. Compromised pregnancies were markedly potentiated when marijuana smoke was combined with a low-protein diet but, conversely, if marijuana smoke was coupled with a high-protein diet some risks associated with the cannabis exposure were attenuated.

IMPACT UPON GROWTH AND NEONATAL AND INFANT BEHAVIOR

As summarized elsewhere[25] most studies have not found cannabis to have a negative impact upon fetal growth. However, in some samples drawn from high-risk environments, a small but significant negative relationship between first trimester cannabis use and birth length[10,42] or birth weight and length[45] have been reported. A limited number of studies have examined growth in offspring of marijuana users beyond the neonatal stage. Those studies which noted a negative association between birth length and prenatal marijuana exposure reported that this association was no longer significant by eight months,[7] one year,[42] or six years.[8] In the OPPS sample, in contrast to newborns born to cigarette-smoking mothers, prenatal exposure to marijuana was not significantly related to any growth measures at birth,[16,25] although a smaller head circumference observed at all ages reached statistical significance among early adolescents born to heavy marijuana users.[25]

The relationship between behavior of the newborn and prenatal cannabis exposure are equivocal. Using the Brazelton Neonatal Behavioral Assessment Scale,[4] in the OPPS sample, at less than one week of age, cannabis was associated with increased fine tremors typically accompanied by exaggerated and prolonged startles, both spontaneous and in response to mild stimuli.[22,11,15] In the same sample, maternal marijuana use was associated with relatively similar observations in 9-and 30-day-old infants.[21] At 9 days, hand-to-mouth behavior was associated with marijuana use during pregnancy. Many of the behaviors seen both in the newborn and at 9 and 30 days are consistent with, but milder in degree, those found among infants undergoing opioid withdrawal.

Habituation, which in infants is an indicator of nervous system functioning and integrity, was associated with prenatal cannabis exposure. In the OPPS sample, newborns of less than a week born to marijuana users had poorer habituation to visual, but not auditory, stimuli.[11,15] In a primate study,[28] behavior distinguishing marijuana offspring from controls was a failure to habituate to novel visual stimuli. At 9 and 30 days of age, no association in the OPPS sample was apparent between maternal marijuana use and visual outcome measures such as pupil dilation and nystagmus. Compared to the remainder of the sample, more babies born to cannabis users demonstrated a lack of visual habituation but the increased incidence did not reach statistical significance.[21]

Findings of altered cry acoustics in a Jamaican cohort[35] and altered sleep-electroencephalograms in a Pittsburgh cohort[41] in newborns of cannabis users are consistent with the OPPS observations of an association between prenatal cannabis and neonatal nervous system functioning. However, no negative relationship between infant behavior and maternal cannabis use was found in the Jamaican[33] and Pittsburgh[40] studies nor in a Denver cohort.[42]

IMPACT BEYOND INFANCY

The literature describing possible neurobehavioral teratogenic effects of maternal use of marijuana beyond infancy is quite sparse. At one year of age, researchers, all using the Bayley Scales of Infant Development,[3] have reported no effect of cannabis use during pregnancy on infant mental or motor development.[42,19,2]

In children involved in the OPPS this lack of effect of prenatal cannabis exposure persisted beyond infancy. At ages two[18] and three,[19] maternal marijuana use was not associated with cognitive outcome variables. However, at age four,[19] memory and verbal outcome measures were negatively associated with maternal marijuana use. These observations are strikingly similar to those reported by Day and associates[9] in which the three-year-old offspring of marijuana users were impaired on the short-term memory, verbal, and abstract/visual reasoning subscales of the Stanford-Binet Intelligence Scale. Griffith et al.[31] also noted, in three-year-old offspring, that maternal marijuana use was predictive of poorer performance on abstract/visual reasoning although use during pregnancy was not associated with an overall lowered IQ.

Reports focusing upon the cognitive effects of prenatal cannabis exposure in offspring older than three years are limited, with two exceptions, to data derived from the OPPS. In five- and six-year-old children from this sample, maternal use of cannabis was not found to be associated with lowered IQ,[17] although at six years of age, prenatal cannabis habits were associ-

ated with increased omission errors on a vigilance task, possibly reflecting a deficit in sustained attention.[23] Furthermore, parental ratings of these children at that age indicated greater problems particularly in the area of inattention and conduct.[38] Leech et al.[34] reported an increase in commission errors and a decrease in omission errors in six-year-olds, associated with second trimester cannabis use. This was interpreted as prenatal marijuana use affecting attention and impulsivity. At ten years of age, in the same sample, Richardson et al.,[39] consistent with the observations in the OPPS sample, observed that prenatal cannabis use predicted higher maternal ratings of the child's inattention, impulsivity, and activity.

IMPACT UPON EXECUTIVE FUNCTION

It has been proposed[12] that in utero cannabis exposure may impact upon certain behaviors/cognitive abilities that fall under the construct of executive function. This term is a shorthand to describe a multiple, nonunitary set of cognitive/behavioral abilities critical in effortful, nonroutine, goal-oriented situations. Behaviors thought to reflect this function[13] include cognitive flexibility in problem solving, focused attention, inhibiting prepotent responses, monitoring, evaluating and adjusting self-directed responses, and working memory (the temporary storage of information while processing incoming data). Most researchers report that this construct is not associated with measures of global intelligence.[13] Underlying this disassociation, at least in part, is that traditional intelligence tests set up specific tasks and goals thus obscuring the assessment of such key aspects of executive function as integration of domains of functioning, goal setting, planning, and self-monitoring.

Components of executive function, including lessened self-regulatory abilities (possibly manifested as behavioral problems), lower scores on tasks of sustained attention, and poorer abstract/visual reasoning, differentiate the offspring of marijuana users from comparison children. The lack of association between prenatal exposure to cannabis and a lowering of general IQ in the offspring[17,12,31] is also consistent with the proposed link between in utero exposure to cannabis and aspects of executive function.

Two recent reports support linking prenatal marijuana exposure to deficits in particular aspects of executive functioning. Fried et al.[24] examined the cognitive performance in 9- to 12-year-old OPPS subjects using a series of tests assessing aspects of executive functioning and the Weschler Intelligence Scale for Children-III (WISC-III) with its subscales, composite, and derived scores.[44] In contrast to children exposed to cigarette smoking, prenatal marijuana exposure was not associated with global intelligence but was negatively associated with the executive function tasks that required impulse control and visual analysis/hypothesis testing and with a number of

WISC subtests requiring the same abilities. These findings are very similar to the impairment in abstract/visual reasoning associated with prenatal marijuana use reported in other cohorts at younger ages.[9,31] A second study was undertaken[20] to further examine prenatal marijuana's impact on integrative visuoperceptual tasks. In the OPPS, nine- to twelve-year-olds were administered tests ranging in complexity from requiring basic visuoperceptual and visuomotor skills to requiring considerable integration and cognitive manipulation of these fundamental skills. Prenatal cannabis exposure was not associated with basic visuoperceptual functioning but was negatively associated with problems requiring the integration of these basic skills. Furthermore, the negative impact of prenatal cannabis exposure on these problem-solving tasks persisted after statistically controlling for the underlying spatial and motor abilities. These findings support the interpretation of prenatal cannabis exposure impacting upon "top-down" integrative, cognitive processes associated with particular facets of executive function.

That only particular facets of executive function are associated with maternal marijuana use is consistent with substantial evidence suggesting that executive function is not of a singular nature. For example, using a factor analytical approach to executive function in children, Welsh et al.[43] reported that, in a battery of tests of this construct administered to a normative sample of children aged three to twelve, three independent factors were revealed. One factor, labeled hypothesis testing and impulse control, defined as requiring visual analysis and inhibition of prepotent responses, is strikingly similar to those associated with prenatal cannabis exposure described above.

From a developmental point of view, executive function is a multistage process with different functions maturing at different ages.[13] Although precursors or rudimentary aspects of executive function are present in infants and toddlers (e.g., object search and object permanence behavior), spheres of executive functioning are not apparent or are difficult to test until the children approach or reach school age and continue to develop at least until puberty.[13,43] Observations at younger ages with the OPPS sample are consistent with this developmental progression for, as described earlier, neurobehavioral effects of cannabis were not noted beyond the neonatal period until the child was four years of age.[19] Furthermore, only at six years of age and not earlier was prenatal cannabis exposure associated with behavioral problems, aspects of attention and visual perceptual tasks.[17] Competence in hypothesis testing and impulse control, in contrast to other aspects of executive function, are reported, in normative studies, to be achieved at 10 years of age[43]—a finding that is consistent with the observation of marijuana's negative effect on this dimension of executive function being manifest in the 9- to 12-year-olds.

CONCLUSION

The consequences of prenatal exposure to cannabis are subtle. The impact during the course of pregnancy and upon the neonate appear to be considerably moderated by other risk factors with evidence from a number of cohorts suggesting mild effects upon fetal growth and central nervous system functioning. During the toddler stage, there is little evidence for a prenatal cannabis effect either upon growth or behavior. However, beyond the age of three, there are suggestive findings indicating a putative association between prenatal marijuana exposure and aspects of cognitive behavior that fall under the rubric of executive function. Particularly, the facets of this construct that appear impacted are the domains of attention/impulsivity and problem solving situations requiring integration and manipulation of basic visuoperceptual skills. Although there is a convergence of evidence, the very limited number of studies which have followed children beyond the age of three emphasizes the need for further, well-controlled investigations in this area.

REFERENCES

1. Abel EL. *Marijuana: The first twelve thousand years*. New York: Plenum Press, 1980.

2. Astley S, Little R. Maternal marijuana use during lactation and infant development at one year. *Neurotoxicology and Teratology* 1990;12(2):161-168.

3. Bayley N. *Bayley Scales of Infant Development*. New York: Psychological Corporation, 1989.

4. Brazelton TB. *Neonatal Behavioral Assessment Scale*. London: William Heinemann and Sons, 1973.

5. Charlebois AT, Fried PA. The interactive effects of nutrition and cannabis upon rat perinatal development. *Developmental Psychobiology* 1980;13(6):591-605.

6. Dalterio SL, Fried PA. The effects of marijuana use on offspring. In Sonderegger TB, ed. *Perinatal substance abuse*. Baltimore: John Hopkins University Press, 1992, pp. 161-183.

7. Day N, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth through 3 years of age. *Neurotoxicology and Teratology* 1992;14(6):407-414.

8. Day NL, Richardson GA, Geva D, Robles N. Alcohol, marijuana, and tobacco: Effects of prenatal exposure on offspring growth and morphology at age six. *Alcoholism, Clinical and Experimental Research* 1994;18(4):786-794.

9. Day N, Richardson G, Goldschmidt L, Robles N, Taylor P, Stoffer D, Cornelius M, Geva D. The effect of prenatal marijuana exposure on the cognitive

development of offspring at age three. *Neurotoxicology and Teratology* 1994;16(2):169-175.

10. Day N, Sambamoorthi U, Taylor P, Richardson G, Robles N, Jhon Y, Scher M, Stoffer D, Cornelius M, Jasperse D. Prenatal marijuana use and neonatal outcomes. *Neurotoxicology and Teratology* 1991;13(3):329-334.

11. Fried PA. Marijuana use by pregnant women and effects on offspring: An update. *Neurotoxicology and Teratology* 1982;4(4):451-454.

12. Fried PA. The Ottawa Prenatal Prospective Study (OPPS): Methodological issues and findings—It's easy to throw the baby out with the bath water. *Life Sciences* 1995;56(23-24):2159-2168.

13. Fried PA. Behavioral evaluation of the older infant and child. In Slikker W Jr, Chang LW, eds. *Handbook of Developmental Neurotoxicology*. San Diego: Academic Press, 1998, pp. 469-486.

14. Fried PA, Buckingham M, Von Kulmiz P. Marijuana use during pregnancy and perinatal risk factors. *American Journal of Obstetrics and Gynecology* 1983;146(8):922-924.

15. Fried PA, Makin JE. Neonatal behavioural correlates of prenatal exposure to marijuana, cigarettes and alcohol in a low risk population. *Neurotoxicology and Teratology* 1987;9(1):1-7.

16. Fried PA, O'Connell CM. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. *Neurotoxicology and Teratology* 1987;9(2):79-85.

17. Fried PA, O'Connell CM, Watkinson B. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes and alcohol: Cognitive and language assessment. *Journal of Developmental and Behavioral Pediatrics* 1992;13(6):383-391.

18. Fried PA, Watkinson B. 12- and 24-month neurobehavioural follow-up of children prenatally exposed to marijuana, cigarettes and alcohol. *Neurotoxicology and Teratology* 1988;10(4):305-313.

19. Fried PA, Watkinson B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes and alcohol. *Journal of Developmental and Behavioral Pediatrics* 1990;11(2):49-58.

20. Fried PA, Watkinson B. Visuoperceptual functioning differs in 9-12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 2000;22(1):11-20.

21. Fried PA, Watkinson B, Dillon RF, Dulberg CS. Neonatal neurological status in a low-risk population after prenatal exposure to cigarettes, marijuana and alcohol. *Journal of Developmental and Behavioral Pediatrics* 1987;8(6):318-326.

22. Fried PA, Watkinson B, Grant A, Knights RK. Changing patterns of soft drug use prior to and during pregnancy: A prospective study. *Drug and Alcohol Dependence* 1980;6(5):323-343.

23. Fried PA, Watkinson B, Gray R. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marijuana, cigarettes and alcohol. *Neurotoxicology and Teratology* 1992;14(5):299-311.

24. Fried PA, Watkinson B, Gray, R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 1998;20(3):293-306.

25. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology*, 1999;21(5):513-525.

26. Fried PA, Watkinson B, Willan A. Marijuana use during pregnancy and decreased length of gestation. *American Journal of Obstetrics and Gynecology* 1984;150(1):23-27.

27. Gibson GT, Bayhurst PA, Colley DP. Maternal alcohol, tobacco and cannabis consumption and the outcome of pregnancy. *Australian and New Zealand Journal of Obstetrics and Gynecology* 1983;23(1):15-19.

28. Golub MS, Sassenrath EN, Chapman CF. Regulation of visual attention in offspring of female monkeys treated chronically with delta-9-tetrahydrocannabinol. *Developmental Psychobiology* 1981;14(6):507-512.

29. Greenland S, Richwald GA, Honda GD. The effects of marijuana use during pregnancy. II. A study in a low risk home-delivery population. *Drug and Alcohol Dependence* 1983;11(3-4):359-366.

30. Greenland S, Staisch KJ, Brown N, Gross SJ. The effects of marijuana use during pregnancy. I. A preliminary epidemiologic study. *American Journal of Obstetrics and Gynecology* 1982;143(4):408-413.

31. Griffith DR, Azuma SD, Chasnoff IJ. Three-year outcome of children exposed prenatally to drugs. *Journal of the American Academy of Child and Adolescent Psychiatry* 1994;33(1):20-27.

32. Hatch EE, Bracken MR. Effects of marijuana use in pregnancy on fetal growth. *American Journal of Epidemiology* 1986;124(6):986-993.

33. Hayes J, Dreher M, Nugent K. Newborn outcomes with maternal use in Jamaican women. *Pediatric Nursing* 1988;14(2):107-110.

34. Leech SL, Richardson G, Goldschmidt L, Day NL. Prenatal substance exposure: Effects on attention and impulsivity of 6-year-olds. *Neurotoxicology and Teratology* 1999;21(2):109-118.

35. Lester B, Dreher M. Effects of marijuana use during pregnancy on new born cry. *Child Development* 1989;60(4):765-771.

36. *National Pregnancy and Health Survey. Drug use among women delivering live births: 1992*. NIH Publication Number 96-3819. Rockville, MD: National Institute on Drug Abuse 1996.

37. O'Connell CM, Fried PA. An investigation of prenatal cannabis exposure and minor physical anomalies in a low risk population. *Neurobehavioral Toxicology and Teratology* 1984;6(5):345-350.

38. O'Connell CM, Fried PA. Prenatal exposure to cannabis: A preliminary report of postnatal consequences in school-age children. *Neurotoxicology and Teratology* 1991;13(6):631-639.

39. Richardson GA, Day NL. A comparison of the effects of prenatal marijuana, alcohol, and cocaine use on 10-year child outcome. *Neurotoxicology and Teratology* 1997;19:257 (abstract).

40. Richardson G, Day N, Taylor P. The effect of prenatal alcohol, marijuana, and tobacco exposure on neonatal behavior. *Infant Behavior and Development* 1989;12:199-209.

41. Scher M, Richardson G, Coble P, Day N, Stoffer D. The effects of prenatal alcohol and marijuana exposure: Disturbances in neonatal sleep cycling and arousal. *Pediatric Research* 1988;24(7):101-105.

42. Tennes K, Avitable N, Blackard C, Boyles C, Hassoun B, Holmes L, Kreye M. Marijuana: Prenatal and postnatal exposure in the human. In Pinkert TM, ed. *NIDA Research Monograph* 1985;59:48-62.

43. Welsh MC, Pennington BF, Grossier DB. A normative-developmental study in executive function: A window on prefrontal function in children. *Developmental Neuropsychology* 1991;7:131-149.

44. Weschler D. *Weschler Intelligence Scale for Children*. Third edition. New York: The Psychological Corporation, 1991.

45. Zuckerman B, Frank D, Hingson R, Amaro H, Levenson S, Kayne H, Parker S, Vinci R, Aboagye K, Fried L, et al. Effects of maternal marijuana and cocaine use on fetal growth. *New England Journal of Medicine* 1989;320(12):762-768.

Chapter 25

Immune System

Guy A. Cabral

IMMUNE SYSTEM AND CANNABINOID RECEPTORS

The role of marijuana, *Cannabis sativa,* in health and infectious disease has been examined for many years. In vivo and in vitro studies have demonstrated that THC is immunosuppressive and impairs cell-mediated immunity, humoral immunity, and cellular defenses against a variety of infectious agents (see the work of Cabral and Pettit[7] and Friedman and Klein[14] for overviews). Two modes of action by which THC and other cannabinoids affect cell functions have been proposed.[13] THC may exert nonspecific effects by perturbing cellular membranes since it is a highly lipophilic molecule. This property of THC may account, in part, for its diverse array of immunosuppressive effects. Alternatively, THC may affect cell function by specific interaction with cannabinoid receptors (see Chapter 7). Two receptor subtypes, CB_1 and CB_2, have been identified in various cells and tissues of the immune system. The CB_1, while preponderant in brain and neural tissue, is present at low levels in immune cells. Transcripts (i.e., mRNA) for the CB_2 are abundant in spleen and tonsils and are found at levels equivalent to those for CB_1 mRNA in the central nervous system.[15,29] However, in other tissues of the immune system, mRNA levels for the CB_2, while exceeding those for the CB_1,[3,29] are relatively low. The distribution pattern of CB_2 mRNA displays major variation in human blood cell populations with a rank order of B lymphocytes > natural killer (NK) cells > monocytes > polymorphonuclear neutrophils > T8 lymphocytes > T4 lymphocytes.[29] A rank order for levels of CB_2 transcripts similar to that for primary human cell types has been recorded for human cell lines belonging to the myeloid, monocytic, and lymphoid lineages (see Table 25.1).[29]

TABLE 25.1. Cannabinoid Receptor Expression in Immune Cells and Tissues

Cell type/tissue	Species	Receptor subtype	Receptor expression detection	Reference
B-lymphocytes	human	CB_2	RT-PCR	14
Lymph nodes	rat	CB*	radioligand binding, radioligand autoradiography	18
Macrophages	human	CB_2	RT-PCR	14
Mast cells	rat	CB_2	RT-PCR	12
Natural killer (NK) cells	human	CB_2	RT-PCR	14
Peripheral mononuclear cells	human, rat	CB_2	RT-PCR	12,13,14
Peyer's Patches	rat	CB*	radioligand binding, radioligand autoradiography	18
Spleen	human, mouse, rat	CB*, CB_1, CB_2	Northern-blot, In-situ-hybridization, radioligand binding, radioligand autoradiography, RT-PCR	12,14,15, 18
CD4+ lymphocytes	human	CB_2	RT-PCR	14
CD8+ lymphocytes	human	CB_2	RT-PCR	14
Tonsils	human	CB_2	immunocytochemistry, RT-PCR	14
Thymus	human	CB_2	RT-PCR	14

Receptor subtype not defined
RT-PCR=reverse transcription polymerase chain reaction

In addition to the identification of cannabinoid receptor mRNA in immune cells, the presence of cognate protein has been demonstrated in rat lymph nodes, Peyer's Patches, and spleen.[23] This protein for the CB_2 has been identified by immunohistochemistry in human tonsil sections using receptor subtype-specific antibodies.[3] It was revealed that protein expression for the CB_2 was limited to B lymphocyte-enriched areas of the mantle of secondary lymphoid follicles.

The apparent sequestration of the CB_2 to cells of the immune system implicates this receptor subtype as playing a role in immune functions. How-

ever, since both the CB_1 and CB_2 are present in immune cells and tissues, functional linkages to the regulation of immune responses cannot be attributed solely to a single receptor subtype and a complex interplay of signal transductional activities may occur.

ANIMAL STUDIES

Data indicative of the immunosuppressive potential of cannabinoids have been obtained primarily from in vitro and animal studies. Guinea pigs and mice have been used extensively as experimental models for documenting the effects of cannabinoids on host resistance in the intact animal. Morahan et al.[28] demonstrated that mice exposed to THC were compromised in their ability to resist infection to herpes simplex virus and *Listeria monocytogenes*. In these studies, high doses of THC were administered to animals through a systemic rather than a natural route such as marijuana smoke. Nevertheless, it was established that THC had the potential for compromising host resistance to both viruses and bacteria. Mishkin and Cabral[27] and Cabral et al.[5] confirmed these results and indicated further that THC decreased resistance to genital herpes simplex virus infection in guinea pigs in a drug dose-dependent fashion, implicating THC as having a direct and specific effect on host resistance. In addition, Mishkin and Cabral[27] demonstrated that the decreased antiviral responsiveness was paralleled by decreased cellular and humoral immunity, suggesting that THC targeted specific elements of the immune system involved in antivirus responses. In addition, THC has been linked to exacerbated murine retroviral-induced immune suppression and infection in mice[32] and to the induction of cytokine-mediated mortality of mice infected with *Legionella pneumophila*.[20] Massi et al.[25] studied the effects of acute and chronic exposure to THC on immune parameters in male Swiss mice. Depressed NK cell activity and decreased interferon gamma ($IFN\gamma$) levels were recorded for animals subjected to acute THC treatment. In the case of animals subjected to chronic THC exposure and shown to be tolerant to this cannabinoid, alterations in immune functional and biochemical parameters in addition to those noted for acute exposure were recorded. Splenocyte proliferative responses, as well as interleukin-2 (IL-2) levels, were reduced.

Studies that have been performed on experimental animals have utilized THC doses in the range of 0.2 to 100 mg/kg. These doses have been administered by different routes to guinea pigs and mice. The concentrations of THC measured in the circulation of these animals are achievable in human marijuana smokers following appropriate extrapolation for mass/surface ratio.[31]

IN VITRO STUDIES

In vitro studies have provided insight as to the specific cellular and subcellular elements of the immune system which are targeted by THC. Cell populations including splenocytes, purified macrophages, and lymphocytes from various rodents and humans, and immortalized cell types exhibiting macrophage-like or T-lymphocyte-like properties, have been examined. THC has been reported to inhibit the ability of macrophages to repress virus replication in cells to which they attach (i.e., extrinsic antiviral activity)[6,8] and to overcome the restriction of the growth of *Legionella pneumophila* within macrophages.[1] In addition, THC has been shown to alter the capacity of macrophages to kill *Naegleria fowleri,*[4] free-living amoebae that can cause a fatal disease in humans known as primary amoebic meningoencephalitis (PAME).[24]

Studies to determine the mechanism by which THC alters macrophage function have indicated that this cannabinoid alters macrophage processing of antigens that is necessary for the activation of CD4+ T lymphocytes.[26] Activated $CD4_+$ helper T cells produce numerous regulatory cytokines critical in the orchestration of various immune functions. Thus, THC-mediated inhibition of antigen processing could result in diminished production of cytokines. Indeed, THC and other cannabinoids have been reported to inhibit their production and secretion. Srivastava et al.[33] examined the effect of THC and cannabidiol (CBD) on cytokine production in vitro by human leukemic T, B, eosinophilic, and CD8+ natural killer lines. THC was found to decrease the constitutive production of interleukin-8 (IL-8), macrophage inflammatory protein-1 alpha (MIP-1 alpha), MIP-1 beta, and regulated upon activation normal T-cell expressed and secreted (RANTES) protein. Phorbol ester-stimulated production of tumor necrosis factor-alpha ($TNF\alpha$), granulocyte-macrophage colony-stimulating factor (GM-CSF), and $IFN\gamma$ produced by NK cells also were affected. These results indicated that THC and the nonpsychotropic cannabinoid CBD affected the production of a multiplicity of cytokines across a diverse array of immune cell lineages. Kaminski et al.[19] examined the signaling pathways affected by THC. It was reported that THC-mediated suppression of humoral immune responsiveness was effected partially through inhibition of adenylate cyclase by a pertussis toxin-sensitive guanine nucleotide binding-protein (G-protein) coupled mechanism. These results are consistent with an implied linkage of a cannabinoid receptor to cannabinoid-mediated inhibition of humoral immunity.

Collectively, in vitro studies have demonstrated that cannabinoids alter the functional activities of a variety of immune cell types and that some of these effects may be linked functionally to cannabinoid receptors.[26] However, there are at present no definitive data which demonstrate that these in vitro cellular effects are operative in humans.

HUMAN DATA WITH CANNABIS/THC

The issue of whether a direct linkage exists between marijuana use and decreased host resistance to infection in humans remains unresolved (see the work of Felder and colleagues[13] and Friedman and Klein[14] for overviews). Studies conducted to determine the effects of marijuana smoking on the immune system have yielded conflicting results. Several human clinical trials in which peripheral blood lymphocytes from healthy individuals and from chronic marijuana smokers were obtained have revealed no differences in mitogen-induced proliferation or rosette formation.[18,22,30,35] Wallace et al.[34] examined risk factors and outcomes associated with identification of *Aspergillus* in respiratory specimens from individuals with HIV disease as part of a study to evaluate pulmonary complications of HIV infection. Cigarette and marijuana use was found not to be associated with *Aspergillus* respiratory infection. DiFranco et al.,[11] through the San Francisco Men's Health Study (SFMHS), evaluated the association of specific recreational drugs and alcohol with laboratory predictors of AIDS. Individuals were assessed at time of entry into the study and with the development of AIDS during six years of follow-up. No association with progression to AIDS was observed for marijuana.

In contrast, other studies have reported that cannabinoids and marijuana exert deleterious effects on immune functionality in humans. Baldwin et al.[2] evaluated the function of alveolar macrophages recovered from the lungs of nonsmokers and habitual smokers of either tobacco, marijuana, or crack cocaine. Alveolar macrophages from marijuana smokers were deficient in their ability to phagocytose *Staphylococcus aureus* and were severely limited in their ability to kill both bacteria and tumor cells. Use of NG-monomethyl-L-arginine monoacetate, an inhibitor of nitric oxide synthetase, in these studies suggested that alveolar macrophages from smokers of marijuana were not able to utilize nitric oxide as an antibacterial effector molecule. Furthermore, alveolar macrophages from marijuana smokers, but not from smokers of tobacco or cocaine, produced less than normal amounts of TNFα, GM-CSF, and interleukin-6 (IL-6) when stimulated with lipopolysaccharide, a potent activator of macrophages. Kusher et al.[21] reported that THC suppressed the functional activities of human large granular lymphocytes (LGL).[21] Exposure of LGL to THC at physiologically relevant concentrations resulted in down regulation of TNFα production and diminished their cytolytic activity against K562 tumor cells. The investigators suggested that, since the natural killer/polymorphonuclear neutrophil axis represents an important early defense against the opportunistic fungus *Candida albicans,* repression of this system could contribute to susceptibility to opportunistic infections. On the other hand, Derocq et al.[10] reported that cannabinoids, rather than exerting inhibitory effects on cellular functions,

enhanced human tonsillar B-cell growth at low nanomolar concentrations. The cannabinoid-enhancing B-cell proliferation was inhibited by pertussis toxin suggesting that a G-protein-coupled receptor process was involved. Since the CB_1 specific antagonist SR141716A had no effect on B-cell proliferation, and human B-cells displayed large amounts of CB_2 mRNAs, it was suggested that the growth enhancing activity was mediated through the CB_2. Collectively, the data suggest that THC may exert either inhibitory or stimulatory effects depending on the cellular system involved and on the dose of THC applied.

One of the earliest indications that marijuana exposure could alter resistance to infections in humans was provided through an anecdotal report by Juel-Jensen.[17] In the report, individuals infected with the herpes simplex virus who were marijuana smokers had an increased recurrence of viral lesions as compared with those who did not smoke marijuana. Subsequently, Gross et al.[16] reported that marijuana use altered responsiveness of human papillomavirus to systemic recombinant interferon alpha-2a (IFNα2a) treatment and suggested that THC could be a cofactor influencing the outcome of infection. In addition, immuno-epidemiological studies using univariant and multivariant analyses have indicated an association between marijuana use and the progression of human immunodeficiency virus (HIV) seropositivity to the development of symptomatic acquired immune deficiency syndrome (AIDS).[34] Whitfield et al.[36] examined the impact of ethanol and Marinol/marijuana on HIV+/AIDS patients undergoing azidothymidine (AZT), azidothymidine/dideoxycytidine (AZT/DDC), or dideoxyinosine (DDI) therapy. Marinol/marijuana was reported to be associated with declining health status in both the AZT and AZT/DDC groups. However, in HIV+/AIDS patients with the lowest CD4+ counts undergoing DDI monotherapy, utilization of Marinol/marijuana did not seem to have a deleterious impact. Caiaffa et al.[9] indicated that smoking illicit drugs such as marijuana was one of several factors which increased risk of bacterial pneumonia in human immunodeficiency virus-seropositive drug users.

In summary, a limited number of controlled longitudinal epidemiological and immunological studies have been undertaken in attempts to correlate the immunosuppressive effects of marijuana smoke or THC on the incidence of infections or viral disease in different segments of the human population. However, results as to whether marijuana or THC exacerbates human resistance to infections, including those with HIV, are inconclusive.

RELEVANCE FOR THE THERAPEUTIC SITUATION IN THERAPEUTIC DOSES

Currently, no recommended dosage for THC or marijuana which is applicable specifically to modulation of immune responsiveness in humans

exists. Therapeutic applications of cannabinoids, including THC, in the immune system are as yet unclear (see the work of Cabral and Pettit[7] and Friedman and Klein[13] for overviews).

REFERENCES

1. Arata S, Newton C, Klein T, Friedman H. Enhanced growth of *Legionella pneumophila* in tetrahydrocannabinol-treated macrophages. *Proceedings of the Society for Experimental Biology and Medicine* 1992;199(1):65-67.

2. Baldwin GC, Tashkin DP, Buckley DM, Park AM, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American Journal of Respiratory and Critical Care Medicine* 1997;156(5): 1606-1613.

3. Bouaboula M, Rinaldi M, Carayon P, Carillon C, Delpech B, Shire D, Le Fur G, Casellas P. Cannabinoid receptor expression in human leukocytes. *European Journal of Biochemistry* 1993;214(1):173-180.

4. Burnette-Curley D, Marciano FM, Fischer K, Cabral GA. Delta-9-tetrahydrocannabinol inhibits cell contact-dependent cytotoxicity of *Bacillus* Calmette-Guérin-activated macrophages. *International Journal of Immunopharmacology* 1993;15(3):371-382.

5. Cabral G, Mishkin EM, Marciano FM, Coleman RE, Harris LS, Munson AE. Effect of delta-9-tetrahydrocannabinol on herpes simplex virus type 2 vaginal infection in the guinea pig. *Proceedings of the Society for Experimental Biology and Medicine* 1986;182(2):181-186.

6. Cabral G, Vásquez R. Effects of marijuana on macrophage function. In Friedman H, Specter S, Klein T, eds. *Drugs of abuse, immunity, and immunodeficiency.* New York: Plenum Press, 1991.

7. Cabral GA, Dove Pettit D. Drugs and immunity: Cannabinoids and their role in decreased resistance to infectious disease. *Journal of Neuroimmunology* 1998; 83(1-2):116-123.

8. Cabral GA, Vásquez R. Delta-9-tetrahydrocannabinol suppresses macrophage extrinsic antiherpesvirus activity. *Proceedings of the Society for Experimental Biology and Medicine* 1992;199(2):255-263.

9. Caiaffa WT, Vlahov D, Graham NM, Astemborski J, Solomon L, Nelson KE, Munoz A. Drug smoking, *Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. *American Journal of Respiratory and Critical Care Medicine* 1994;150(6 Pt 1):1493-1498.

10. Derocq JM, Segui M, Marchand J, Le FG, Casella P. Cannabinoids enhance human B-cell growth at low nanomolar concentrations. *FEBS Letters* 1995;369(2-3):177-182.

11. DiFranco MJ, Sheppard HW, Hunter DJ, Tosteson TD, Ascher MS. The lack of association of marijuana and other recreational drugs with progression to AIDS

in the San Francisco Men's Health Study. *Annals of Epidemiology* 1996;6(4):283-289.

12. Facci L, Dal Toso R, Romanello S, Buriani A, Skaper SD, Leon A. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. *Proceedings of the National Academy of Sciences,* USA 1995;92(8):3376-3380.

13. Felder CC, Veluz JS, Williams HL, Briley EM, Matsuda LA. Cannabinoid agonists stimulate both receptor- and non-receptor-mediated signal transduction pathways in cells transfected with and expressing cannabinoid receptor clones. *Molecular Pharmacology* 1992;42(5):838-845.

14. Friedman H, Klein TW. Marijuana and immunity. *Science and Medicine* 1999;6(2):12-21.

15. Galiègue S, Mary S, Marchand J, Dussosoy D, Carrière D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry* 1995;232(1):54-61.

16. Gross G, Roussaki A, Ikenberg H, Dress N. Genital warts do not respond to systemic recombinant interferon alpha-2a treatment during cannabis consumption. *Dermatology* 1991;183(3):203-207.

17. Juel-Jensen BE. Cannabis and recurrent herpes simplex. *British Medical Journal* 1972;iv:296.

18. Kaklamani E, Trichopoulos D, Koutselinis A, Drouga M, Karalis D. Hashish smoking and T-lymphocytes. *Archives of Toxicology* 1978;40(2):97-101.

19. Kaminski NE, Koh WS, Yang KH, Lee M, Kessler FK. Suppression of the humoral immune response by cannabinoids is partially mediated through inhibition of adenylate cyclase by a pertussis toxin-sensitive G-protein coupled mechanism. *Biochemical Pharmacology* 1994;48(10):1899-1908.

20. Klein T, Newton C, Widen R, Friedman H. Delta-9-tetrahydrocannabinol injection induces cytokine-mediated mortality of mice infected with *Legionella pneumophila*. *Journal of Pharmacology and Experimental Therapeutics* 1993; 267(2):635-640.

21. Kusher DI, Dawson LO, Taylor AC, Djeu JY. Effect of the psychoactive metabolite of marijuana, delta-9-tetrahydrocannabinol (THC), on the synthesis of tumor necrosis factor by human large granular lymphocytes. *Cellular Immunology* 1994;154(1):99-108.

22. Lau RJ, Tubergen DG, Barr M Jr, Domino EF, Benowitz N, Jones RT. Phytohemagglutinin-induced lymphocyte transformation in humans receiving delta-9-tetrahydrocannabinol. *Science* 1976;192(4247):805-807.

23. Lynn AB, Herkenham M. Localization of cannabinoid receptors and nonsaturable high-density cannabinoid binding sites in peripheral tissues of the rat: Implications for receptor-mediated immune modulation by cannabinoids. *Journal of Pharmacology and Experimental Therapeutics* 1994;268(3):1612-1623.

24. Marciano-Cabral F. Biology of *Naegleria* spp. *Microbiological Reviews* 1988;52(1):114-133.

25. Massi P, Sacerdote P, Ponti W, Fuzio D, Manfredi B, Vigano D, Rubino T, Bardotti M, Parolaro D. Immune function alterations in mice tolerant to delta-9-tetrahydrocannabinol: Functional and biochemical parameters. *Journal of Neuroimmunology* 1998;92(1-2):60-66.

26. McCoy KL, Gainey D, Cabral GA. Δ^9-tetrahydrocannabinol modulates antigen processing by macrophages. *Journal of Pharmacology and Experimental Therapeutics* 1995;273(3):1216-1223.

27. Mishkin EM, Cabral G. Delta-9-tetrahydrocannabinol decreases host resistance to herpes simplex virus type 2 vaginal infection in the B6C3F1 mouse. *Journal of General Virology* 1985;66(pt.12):2539-2549.

28. Morahan PS, Klykken PC, Smith SH, Harris LS, Munson AE. Effects of cannabinoids on host resistance to *Listeria monocytogenes* and herpes simplex virus. *Infection and Immunity* 1979;23(3):670-674.

29. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993;365(6447):61-65.

30. Rachelefsky GS, Opelz G. Normal lymphocytes function in the presence of delta-9-tetrahydrocannabinol. *Clinical Pharmacology and Therapeutics* 1977; 21(1):44-46.

31. Rosenkrantz H. The immune response and marijuana. In Nahas GG, Paton WDM, Idanpaan-Heikkila J, eds. *Marijuana: Biological effects, analysis, cellular responses, reproduction and brain*. New York: Pergamon Press, 1976.

32. Specter S, Lancz G, Westrich G, Friedman H. Delta-9-tetrahydrocannabinol augments murine retroviral induced immunosuppression and infection. *International Journal of Immunopharmacology* 1991;13(4):411-417.

33. Srivastava MD, Srivastava BI, Brouhard B. Delta-9-tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells. *Immunopharmacology* 1998;40(3):179-185.

34. Tindall B, Cooper DA, Donovan B, Barnes T, Philpot CR, Gold J, Penny R. The Sydney AIDS Project: Development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. *Australian and New Zealand Journal of Medicine* 1988;18(1):8-15.

35. Wallace JM, Lim R, Browdy BL, Hopewell PC, Glassroth J, Rosen MJ, Reichman LB, Kvale PA. Risk factors and outcomes associated with identification of *Aspergillus* in respiratory specimens from persons with HIV disease. Pulmonary complications of HIV infection study group. *Chest* 1998;114(1):131-137.

36. Whitfield RM, Bechtel LM, Starich GH. The impact of ethanol and Marinol/marijuana usage on HIV+/AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, or dideoxyinosine therapy. *Alcoholism, Clinical and Experimental Research* 1997;21(1):122-127.

Chapter 26

Hormonal System and Reproduction

Laura L. Murphy

The effects of cannabinoids on endocrine and neuroendocrine function and on hormone release are well documented. Some of the earliest work reported the effects of long-term smoking of cannabis on the reproductive endocrine system of the human male[15,16,21,22] and, later, the female. Because cannabinoid-induced alterations in hormone levels might affect reproductive function, i.e., fertility and libido, of males and females, there was considerable interest to pursue this area of research. More detailed information was obtained from animal studies which have confirmed findings in the human, as well as ascertained important information on the site and mechanisms of cannabinoid action with respect to their reproductive and neuroendocrine modulatory effects. There has been less focus in humans and animals on how short- or long-term exposure to cannabis affects endocrine parameters other than the reproductive endocrine system (i.e., stress axis, thyroid, and other metabolic hormones). However, the profound effects that cannabinoids have on the brain and its neurotransmitters, and the hypothalamus and pituitary hormone secretion, would suggest that the endocrine system as a whole is potentially vulnerable to direct or indirect cannabinoid action.

REPRODUCTIVE ENDOCRINE SYSTEM

Males

In the male, basal secretion of the gonadotropin luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland is essential in maintaining testicular spermatogenesis and testosterone secretion. In human males, cannabis smoking has been shown to decrease serum LH, FSH, and testosterone levels when compared to hormone levels in nonsmoking controls[21,22] or presmoking baseline levels.[9] More-

over, an increased incidence of oligospermia has been reported in men who were heavy marijuana smokers.[16,22] Other studies did not find measurable differences in gonadotropin or testosterone secretion in men who were light or heavy marijuana users.[6,12] Animal studies largely confirm the ability of cannabinoids to inhibit gonadotropin and testicular steroid release in the male. Acute THC treatment produces a consistent and significant dose- and time-related decrease in circulating LH and testosterone levels in male rodents.[39] In the male rhesus monkey, an acute dose of THC produced a 65 percent reduction in plasma testosterone levels by 60 min of treatment that lasted for approximately 24 h.[38] Moreover, long-term cannabinoid exposure in male mice disrupted spermatogenesis and induced aberrations in sperm morphology.[44] These studies suggest that THC inhibits LH and FSH secretion, consequently decreasing testosterone production and altering spermatogenesis. The discrepancies that exist in the hormonal response to cannabinoids in men and between humans and animals have yet to be reconciled. Methodological differences in experimental design and the possible development of tolerance[38] to the hormone-altering effects of cannabinoids in men who were long-term and heavy smokers of marijuana may be involved.

The brain is the most likely site of cannabinoid action in the ability of marijuana to alter hormone secretion.[30] THC binds to dense populations of cannabinoid CB_1 receptors in the brain which appear to be involved in the modulation of neurotransmitter release.[7] There is good evidence that the neurotransmitter systems involved in regulation of gonadotropin-releasing hormone (GnRH), i.e., norepinephrine, dopamine, serotonin, GABA, are significantly altered following acute cannabinoid exposure.[28,30]

Cannabinoids can also have a direct testicular action that, particularly with long-term cannabinoid exposure, may play a significant role in the occurrence of lowered testosterone levels and abnormal sperm number and morphology. This is supported by findings that high-dose marijuana smoking in humans has been reported to decrease sperm number in the absence of a corresponding decrease in LH, FSH, or testosterone levels.[16] In in vitro studies with isolated rat Sertoli cells, cannabinoid exposure inhibited the Sertoli cell response to FSH.[31] Using isolated mouse Leydig cells, cannabinoids were shown to directly inhibit testosterone production.[8,10] Recently, cannabinoid-receptor mRNA has been shown to be localized within human testes,[14] suggesting the presence of cannabinoid receptors within testicular tissue. Germ cells may be one site where cannabinoid receptors are localized. Sperm cells obtained from the sea urchin exhibit a dose-related inhibition of the acrosome reaction when exposed to cannabinoids.[36]

Clinical relevance. The use of prescription THC (Marinol) in the marijuana-naive male may cause a transient decrease in plasma levels of LH and testosterone, which could influence libido and potency. With continued us-

age, prescription THC may lead to oligospermia and increased incidence of abnormal sperm morphology; thus, fertility could be compromised. The development of tolerance to the effects of long-term use of THC on testosterone levels has been shown in animal studies and implicated in humans.

Females

A number of well-controlled studies have been performed to determine the effects of marijuana smoking on hormone secretion in cycling and menopausal women. Women who had abstained from smoking marijuana for a least two weeks, smoked a marijuana cigarette containing 1.8 percent THC during the follicular phase, luteal phase, or periovulatory phase of the menstrual cycle. When the marijuana cigarette was smoked during the luteal phase, there was a 30 percent suppression of plasma LH levels within an hour of smoking when compared to placebo-smoking control subjects.[26] Moreover, there were no changes in plasma LH levels following marijuana smoking by women in their follicular phase of the cycle,[26] or in postmenopausal women.[25] Interestingly, there was a significant increase in plasma LH levels when women smoked the marijuana cigarette during the periovulatory phase.[27] These results indicate that the stage of the menstrual cycle dictates a woman's hormonal response to marijuana smoking. Interestingly, estrogen and progesterone differentially modulate the density of cannabinoid receptors in the hypothalamus of female rats,[33] suggesting that fluctuations in circulating estrogen and progesterone levels during the menstrual cycle may influence a woman's responsiveness to cannabinoid as a result of steroid-induced changes in brain cannabinoid receptor.

Studies in female monkeys and rodents largely confirm the findings in human females. An acute injection of THC during the luteal phase of the menstrual cycle significantly reduced circulating progesterone levels.[37] When THC was administered for 18 days during the follicular and preovulatory phases of the menstrual cycle, the preovulatory estrogen and LH surges were blocked and ovulation did not occur during the treatment cycle or in the following posttreatment cycle.[2] The long-term exposure of female monkeys to thrice weekly injections of THC resulted in a disruption of menstrual cycles that lasted for several months and was characterized by decreased LH and sex steroid hormone levels and anovulation.[37] After approximately one year of THC treatment, a tolerance to the reproductive effects of the drug appeared to occur and normal menstrual cycles were spontaneously reestablished. Similarly, in female rats, acute THC exposure decreased basal LH levels[41] and blocked the preovulatory LH and FSH surges when administered during the afternoon of proestrus.[3]

The ability of specific cannabinoid receptor ligands, i.e., CP55940, WIN55212, and anandamide, to inhibit LH release in female rats indicates that cannabinoid receptors mediate the neuroendocrine actions of THC and

other cannabinoids.[30] In the female, as in the male, the primary target of cannabinoid action is the brain, where administered cannabinoids interact with cannabinoid receptors that modulate neurotransmitter/neuropeptide activity and, consequently, GnRH release. Pretreatment of ovariectomized rats with either a serotonin 5-HT_{1A} or a corticotropin-releasing hormone (CRH) receptor antagonist significantly reduces the effects of THC on LH release.[29] Thus, there may be several neuromodulatory systems altered as a result of cannabinoid exposure, any or all of which contribute to the inhibition of gonadotropin secretion.

Cannabinoids have a primarily inhibitory effect on prolactin release in female animals. Acute cannabinoid exposure inhibits basal prolactin release in monkeys[1] and rats,[19] and blocks the prolactin surge which occurs on the afternoon of proestrus[3] or in response to suckling.[40] The hypothalamic tuberoinfundibular dopamine system is predominately responsible for the regulation of prolactin release from the anterior pituitary gland. Acute cannabinoid exposure significantly increases the activity of this neuronal system and increases dopamine release, resulting in decreased prolactin secretion from the pituitary.[34,24]

Clinical relevance. In the drug-naive female, short-term use of prescription THC may cause transient decreases in plasma levels of LH, prolactin, estrogen, and progesterone which could lead to shortened menstrual cycle length and an increased incidence of anovulatory cycles.[5] The development of tolerance to the long-term effects of THC on gonadotropin and ovarian sex steroid concentrations has been shown in the rhesus monkey and has been implicated in humans.

STRESS HORMONE AXIS

Smoking marijuana or the administration of an acute dose of cannabinoid stimulates the release of hypothalamic CRH,[42] pituitary adrenocorticotropic hormone (ACTH[35]), and glucocorticoids[9,35] in experimental animals and humans. An acute dose of THC produces a rapid increase in ACTH and corticosterone levels in female rats.[20] In male rhesus monkeys, acute exposure to marijuana smoke produced a 178 percent increase in urinary cortisol and a 31 percent increase in plasma cortisol levels over pre-exposure hormone levels.[4] Although some tolerance developed to the marijuana smoke exposure after one month, cortisol levels remained elevated throughout the year-long treatment period. Human users of marijuana exposed to an acute dose of oral THC[12] or marijuana cigarettes,[9] exhibited either no change or an increase in circulating cortisol levels, respectively. However, in men and women who were chronic marijuana smokers, basal cortisol levels were not different when compared to a group of non-marijuana smokers.[6] The reason for the differences in corticosteroid response to cannabinoids is unclear;

however, a rapid development of tolerance to cannabinoids has been shown to occur [4,35] and may help explain the differences in the stress hormone response to cannabinoids.

There is increasing evidence that CB_1 receptor activation and alterations in neurotransmitter modulation of CRH secretion mediate the cannabinoid-induced stimulation of ACTH and glucocorticoid release. Autoradiography studies have demonstrated the presence of CB_1 receptors in several hypothalamic nuclei, notably the paraventricular nuclei, a predominant site of CRH neuronal cell bodies.[13] Furthermore, acute or chronic THC administration in rats has pronounced effects on the activity of those neurotransmitter systems closely involved in the regulation of CRH release, including serotonin, norepinephrine, and dopamine.[24,30] The acute administration of anandamide produces a rapid increase in expression of the immediate-early gene *c-fos* in the paraventricular hypothalamus of rats.[43] This suggests that cannabinoids, either directly or indirectly via neurotransmitters, cause neuronal activation within the paraventricular nuclei, leading to CRH activation and release.

Clinical relevance. Acute or short-term exposure to prescription THC may cause activation of the hypothalamic-pituitary-adrenal axis in humans and consequent endocrine, autonomic, and behavioral responses. These may include increased plasma ACTH and cortisol levels, changes in heart rate, altered food intake, and increased anxiety. Good evidence exists for a development of tolerance to long-term effects of THC on plasma ACTH and corticosteroid levels in experimental animals, which may extend to humans as well.

OTHER HORMONES

Systemic or intracerebroventricular administration of cannabinoid decreases plasma growth hormone (GH) levels in experimental animals.[11,24,32] The cannabinoid-induced decrease in GH levels may be preceded by a transient but significant increase in GH release.[32] The ability of HU-210 to produce a dose-related decrease in plasma GH levels indicates that cannabinoid receptors most likely mediate the effect.[24] In vitro studies have demonstrated that THC causes significant stimulation of somatostatin release from hypothalamic fragments,[32] suggesting a role for somatostatin in the inhibition of GH by cannabinoids.

Acute administration of THC reduces serum thyroid-stimulating hormone (TSH) levels by 90 percent within 60 min of treatment in rats.[17] THC treatment did not alter hypothalamic levels of TRH, suggesting that cannabinoids directly influence TSH or thyroid hormone levels.[17]

Glucose tolerance may be impaired following acute exposure to THC in humans.[18] In a study by Hollister, decreased glucose tolerance was accom-

panied by an increase in GH, which implies that GH may be interfering with insulin action.[18] In rabbits, acute THC administration produces hyperglycemia via an epinephrine-dependent pathway.[18] In a study using isolated pancreatic islets from rats, basal insulin secretion and the insulin response to a submaximal dose of glucose were significantly increased following THC treatment.[23]

Clinical relevance. Prescription THC may produce alterations in the plasma levels of a number of metabolic hormones, including GH, TSH, and insulin. Thus, the regulation of blood glucose levels may be affected. This may be of particular concern to individuals with metabolic diseases such as diabetes.

REFERENCES

1. Asch RH, Smith CG, Siler-Khodr TM, Pauerstein C. Acute decreases in serum prolactin concentrations caused by delta-9-tetrahydrocannabinol in nonhuman primates. *Fertility and Sterility* 1979;32(5):571-575.

2. Asch RH, Smith CG, Siler-Khodr TM, Pauerstein CJ. Effects of Δ^9-tetrahydrocannabinol during the follicular phase of the rhesus monkey *(Macaca mulatta). Journal of Clinical Endocrinology and Metabolism* 1981;52(1):50-55.

3. Ayalon D, Nir I, Cordova T, Bauminger S, Puder M, Naor Z, Kashi R, Zor U, Harell A, Lindner HR. Acute effects of Δ^1-tetrahydrocannabinol on the hypothalamo-pituitary-ovarian axis in the rat. *Neuroendocrinology* 1977;23(1):31-42.

4. Bailey JR, Paule MG, Ali SF, Scallet AC, Slikker W. Chronic marijuana smoke exposure in the rhesus monkey II. Effects on urinary cortisol, plasma cortisol and plasma testosterone concentrations. In *1990 Symposium on the Cannabinoids.* Burlington, VT: International Cannabinoid Research Society, 1990, p. 12.

5. Bauman JE. Marijuana and the female reproductive system. In *Health consequences of marijuana use.* Washington, DC: U.S. Government Printing Office, 1980, pp. 85-97.

6. Block RI, Farinpour R, Schlechte JA. Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women. *Drug and Alcohol Dependence* 1991;28(2):121-128.

7. Breivogel CS, Childers SR. The functional neuroanatomy of brain cannabinoid receptors. *Neurobiology of Disease* 1998;5(6 Pt. B):417-431.

8. Burstein S, Hunter SA, Shoupe TS, Taylor P. Cannabinoid inhibition of testosterone synthesis by mouse Leydig cells. *Research Communications in Chemical Pathology and Pharmacology* 1978;19(3):557-560.

9. Cone EJ, Johnson RE, Moore JD, Roache JD. Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. *Pharmacology, Biochemistry and Behavior* 1986;24(6):1749-1754.

10. Dalterio S, Bartke A, Mayfield D. Effects of Δ^9-tetrahydrocannabinol on testosterone production in vitro: Influence of Ca^{++}, Mg^{++}, or glucose. *Life Sciences* 1985;37(15):1425-1433.

11. Dalterio SL, Michael SD, Macmillan BT, Bartke A. Differential effects of cannabinoid exposure and stress on plasma prolactin, growth hormone and corticosterone levels in male mice. *Life Sciences* 1981;28(7):761-766.

12. Dax EM, Pilotte NS, Adler WH, Nagel JE, Lange WR. The effects of 9-ene-tetrahydrocannabinol on hormone release and immune function. *Journal of Steroid Biochemistry* 1989;34(1-6):263-270.

13. Fernández-Ruiz JJ, Muñoz RM, Romero J, Villanúa MA, Makriyannis A, Ramos JA. Time course of the effects of different cannabimimetics on prolactin and gonadotrophin secretion: Evidence for the presence of CB_1 receptors in hypothalamic structures and their involvement in the effects of cannabimimetics. *Biochemical Pharmacology* 1997;53(12):1919-1927.

14. Gerard CM, Mollereau C, Vassart G, Parmentier M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochemical Journal* 1991;279(Pt.1):129-134.

15. Harmon J, Aliapoulios MA. Gynecomastia in marihuana users. *New England Journal of Medicine* 1972;287(18):936.

16. Hembree WC, Zeidenberg P, Nahas GG. Marihuana's effects on human gonadal function. In Nahas GG, ed. *Marihuana, chemistry, biochemistry and cellular effects*. New York: Springer-Verlag, 1976, pp. 521-532.

17. Hillard CJ, Farber NE, Hagen T, Bloom AS. The effects of Δ^9-THC on serum thyrotropin levels in the rat. *Pharmacology, Biochemistry and Behavior* 1984; 20(4):547-550.

18. Hollister LE. Health aspects of cannabis. *Pharmacological Reviews* 1986;38(1): 1-20.

19. Hughes CL, Everett JW, Tyrey L. Δ^9-Tetrahydrocannabinol suppression of prolactin secretion in the rat: Lack of direct pituitary effect. *Endocrinology* 1981; 109(3):876-880.

20. Jackson AL, Murphy LL. Role of the hypothalamic-pituitary-adrenal axis in the suppression of luteinizing hormone release by delta-9-tetrahydrocannabinol. *Neuroendocrinology* 1997;65(6):446-452.

21. Kolodny RC, Lessin P, Toro G, Masters WH, Cohen S. Depression of plasma testosterone with acute marijuana administration. In Braude MC, Szara S, eds. *The Pharmacology of Marijuana*. New York: Raven Press, 1976, pp. 217-225.

22. Kolodny RC, Masters WH, Kolodny RM, Toro G. Depression of plasma testosterone levels after chronic intensive marihuana use. *New England Journal of Medicine* 1974;290(16):872-874.

23. Laychock SG, Hoffman JM, Meisel E, Bilgin S. Pancreatic islet arachidonic acid turnover and metabolism and insulin release in response to delta-9-tetrahydrocannabinol. *Biochemical Pharmacology* 1986;35(12):2003-2008.

24. Martín-Calderón JL, Muñoz RM, Villanúa MA, del Arco I, Moreno JL, Rodríguez de Fonseca F, Navarro M. Characterization of the acute endocrine actions of (-)-11-hydroxy-Δ^8-tetrahydrocannabinol-dimethylheptyl (HU-210), a potent synthetic cannabinoid in rats. *European Journal of Pharmacology* 1998;344(1):77-86.

25. Mendelson JH, Cristofaro P, Ellingboe J, Benedikt R, Mello NK. Acute effects of marihuana on luteinizing hormone in menopausal women. *Pharmacology, Biochemistry and Behavior* 1985;23(5):765-768.

26. Mendelson JH, Mello NK, Ellingboe J, Skupny AST, Lex BW, Griffin M. Marihuana smoking suppresses luteinizing hormone in women. *Journal of Pharmacology and Experimental Therapeutics* 1986;237(3):862-866.

27. Mendelson JH, Mello NK. Effects of marijuana on neuroendocrine hormones in human males and females. In Braude MC, Ludford JP, eds. *Marijuana Effects on the Endocrine and Reproductive Systems*. Washington, DC: US Government Printing Office, 1984, pp. 97-109.

28. Miguel R, Romero J, Munoz RM, Garcia-Gil L, Gonzalez S, Villanua MA, Makriyannis Λ, Ramos JΛ, Fernandez-Ruiz JJ. Effects of cannabinoids on prolactin and gonadotrophin secretion: Involvement of changes in hypothalamic gamma-aminobutyric acid (GABA) inputs. *Biochemical Pharmacology* 1998;56(10):1331-1338.

29. Murphy LL, Λdrian BΛ, Kholi M. Inhibition of luteinizing hormone secretion by Δ^9-tetrahydrocannabinol in the ovariectomized rat: Effect of pretreatment with neurotransmitter or neuropeptide receptor antagonists. *Steroids* 1999; 64(9):664-671.

30. Murphy LL, Muñoz RM, Adrian BA, Villanúa MA. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. *Neurobiology of Disease* 1998;5:432-446.

31. Newton SC, Murphy LL, Bartke A. In vitro effects of psychoactive and non-psychoactive cannabinoids on immature rat Sertoli cell function. *Life Sciences* 1993;53(18):1429-1437.

32. Rettori V, Wenger T, Snyder G, Dalterio S, McCann SM. Hypothalamic action of delta-9-tetrahydrocannabinol to inhibit the release of prolactin and growth hormone in rat. *Neuroendocrinology* 1988;47(6):498-503.

33. Rodríguez de Fonseca F, Cebeira M, Ramos JA, Martin M, Fernández-Ruiz JJ. Cannabinoid receptors in rat brain areas: Sexual differences, fluctuations during estrous cycle and changes after gonadectomy and sex steroid replacement. *Life Sciences* 1994;54(3):159-170.

34. Rodríguez de Fonseca F, Fernández-Ruiz JJ, Murphy LL, Cebeira M, Steger RW, Bartke A, Ramos JA. Acute effects of Δ-^{9}-tetrahydrocannabinol on dopaminergic activity in several rat brain areas. *Pharmacology, Biochemistry and Behavior* 1992;42(2):269-275.

35. Rodríguez de Fonseca F, Murphy LL, Bonnin A, Eldridge JC, Bartke A, Fernández-Ruiz JJ. Δ^9-tetrahydrocannabinol administration affects anterior pitu-

itary, corticoadrenal and adrenomedullary functions in male rats. *Neuroendocrinology (Life Sciences Advances)* 1992;11:147-156.

36. Schuel H, Goldstein E, Mechoulam R, Zimmerman AM, Zimmerman S. Anandamide (arachidonylethanolamide), a brain cannabinoid receptor agonist, reduces fertilizing capacity in sea urchins by inhibiting the acrosome reaction. *Proceedings of the National Academy of Sciences of the United States of America* 1994;91(16):7678-7682.

37. Smith CG, Almirez RG, Berenberg J, Asch RH. Tolerance develops to the disruptive effects of Δ^9-tetrahydrocannabinol on primate menstrual cycle. *Science* 1983;219(4591):1453-1455.

38. Smith CG, Moore CE, Besch NF, Besch PK. The effect of marihuana (delta-9-tetrahydrocannabinol) on the secretion of sex hormones in the mature male rhesus monkey. *Clinical Chemistry* 1976;22:1184.

39. Steger RW, Murphy LL, Bartke A, Smith MS. Effects of psychoactive and nonpsychoactive cannabinoids on the hypothalamic-pituitary axis of the adult male rat. *Pharmacology, Biochemistry and Behavior* 1990;37(2):299-302.

40. Tyrey L, Hughes CL. Inhibition of suckling-induced prolactin secretion by delta-9-tetrahydrocannabinol. In Agurell S, Dewey WL, Wilette RE, eds. *The cannabinoids: Chemical, pharmacologic and therapeutic aspects*. San Diego: Academic Press, 1984, pp. 487-495.

41. Tyrey L. Δ^9-tetrahydrocannabinol: A potent inhibitor of episodic luteinizing hormone secretion. *Journal of Pharmacology and Experimental Therapeutics* 1980;213(2):306-308.

42. Weidenfeld J, Feldman S, Mechoulam R. Effect of the brain constituent anandamide, a cannabinoid receptor agonist, on the hypothalamo-pituitary-adrenal axis in the rat. *Neuroendocrinology* 1994:59(2):110-112.

43. Wenger T, Jamali KA, Juaneda C, Leonardelli J, Tramu G. Arachidonyl ethanolamide (anandamide) activates the parvocellular part of hypothalamic paraventricular nucleus. *Biochemical and Biophysical Research Communications* 1997;237(3):724-728.

44. Zimmerman AM, Zimmerman S, Raj AY. Effects of cannabinoids on spermatogenesis in mice. In Nahas GG, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999, pp. 347-357.

Chapter 27

Long-Term Effects of Cannabis on Psyche and Cognition

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EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Cannabis exerts its most prominent effects on the central nervous system (CNS), whether smoked or ingested, through a specific cannabinoid receptor system.[8,25,34,59] It is primarily for its mind-altering or psychoactive properties that it is used recreationally in many parts of the world. Human studies of the acute effects of cannabis suggest that the cannabinoid receptor system may be involved in regulating mood, emotion, attention, memory, and many other cognitive functions (see Chapter 22). What is not yet certain is the extent to which any of these functions, and indeed the endogenous cannabinoid system and receptor itself, are affected by the prolonged use of exogenous cannabinoids. The evidence to date from both human and animal research suggests that cannabis does not cause gross impairment in the long term, but that there are alterations in their function. This review will briefly present the evidence for long-term effects of cannabis on the CNS and its functions, with focus on recent studies pertinent to the human notions of psyche and cognition (for details and specific citations, see the work of Solowij,[52] as well as that of Adams and Martin,[1] and Childers and Breivogel[6]).

EVIDENCE FROM ANIMAL RESEARCH

Animal research into the effects of cannabis on CNS function has typically administered known quantities of cannabinoids to animals for a specified time and then examined performance on various tasks, before using histological and morphometric methods to study the brains of the exposed

animals. Animal research enables specificity in attribution of effects to cannabinoids by excluding various confounding factors. Extrapolation of the findings directly to humans is, however, difficult, because of differences in brain and behavior, patterns of use, routes of administration, and dosage and methods of assessment. In general, the results of studies with primates produce data that most closely resemble the likely effects in humans.

Overall, surprisingly few animal studies of neurotoxicity have been published and the results have been equivocal. A recent study showed that relatively large doses of THC applied directly to cultured rat hippocampal neurons resulted in significant toxicity and cell death.[4] Some evidence exists for long-term changes in hippocampal ultrastructure and morphology in rodents and monkeys following chronic administration of THC. Several studies of rhesus monkeys in which administered doses were comparable to those used by human heavy cannabis users have reported permanent alterations in brain function and ultrastructure after only a few months' exposure,[24] and brain atrophy, particularly in frontal regions, with long-term exposure (e.g., five years[35]). Other animal studies have found no major abnormalities (or even neuronal protection—see Conclusion), but there have been large differences in the methodology employed, including the doses given and the duration of administration.

Cannabinoids can cause marked changes in brain electrophysiology. Recent animal electroencephalographic (EEG) studies have demonstrated a role for the endogenous cannabinoid system in the sleep/wakefulness cycle.[37] Cannabinoids interact with most neuromodulator systems.[41] The small number of animal studies that have examined brain chemistry following chronic treatment with cannabinoids suggest few if any *irreversible* effects.[51] Although the acute administration of cannabinoids can increase dopaminergic activity, prefrontal cortical dopamine metabolism is reduced in rats following repeated exposure to THC,[26] and reduced dopaminergic transmission in the limbic system is associated with withdrawal from chronic cannabinoid administration in rats.[9]

Rats administered cannabinoids for about three months have shown deficits in memory and learning similar to those observed with damage to or even complete removal of the hippocampus. These deficits have sometimes been shown to persist for up to several months after administration of cannabinoids ceased, although tolerance to such effects has also been demonstrated after 35 days of administration.[7] Tolerance to cannabinoids can be mediated by a downregulation of receptors,[40] but effects on receptor function may occur without consistent changes in the number of receptor-binding sites.[49]

Compelling evidence that the cannabinoid-induced memory impairment is indeed receptor-mediated has been provided by the complete reversal of such impairment by the cannabinoid antagonist SR141716A.[30,33] Anandamide, the

endogenous ligand, has also been shown to dose-dependently impair working memory in rats,[32] and there is evidence that the endogenous cannabinoid system is involved in forgetting and memory deterioration associated with aging.[55]

Chronic administration of cannabinoids has been shown to produce lethargy, sedation, and depression in a number of species, and is taken as evidence of the so-called "amotivational syndrome" which has been difficult to prove in humans. Rhesus monkeys chronically exposed to cannabis for less than one year developed a decreased motivation to respond in a well-learned operant task.[51] This occurred in monkeys exposed to cannabis smoke daily, but was maximal in monkeys exposed only on weekends, suggesting that problems with motivation could occur at relatively low or at "recreational" levels of human use. Performance returned to normal several months after exposure to cannabis smoke ceased. Recovery from memory deficits has also mostly been shown to occur sometime after administration of cannabinoids ceases, but the results of animal studies may not reflect the gradual changes that could occur to the endogenous system over a period of much longer exposure to the drug.

EVIDENCE FROM HUMAN RESEARCH

No evidence from human studies of any structural brain damage following prolonged exposure to cannabinoids exists. Recent studies of human brain postmortem have reported reduced binding and decreased cannabinoid receptor density with disease and normal aging, but no studies have yet examined the brains of chronic cannabis users. Altered brain function and metabolism in humans have been demonstrated following acute and chronic use of cannabis by EEG, cerebral blood flow (CBF), and positron emission tomographic (PET) techniques. The greatest alterations occur in prefrontal and cerebellar regions.

To date, only a single study has investigated neuromodulator levels in human cannabis users and found no alteration of monoamine levels in cerebrospinal fluid (CSF),[38] but this study was riddled with factors that would not enable a proper conclusion to be drawn. Interestingly, new research has found elevated levels of anandamide in the CSF of a small sample of people with schizophrenia.[29] This may reflect a compensation mechanism for the elevated dopamine levels in the brain and might explain why people with schizophrenia often smoke cannabis, supposedly in an attempt to alleviate their symptoms. Alternatively, it was suggested that an imbalance of endogenous cannabinoids may contribute to the pathogenesis of schizophrenia. This would be of particular concern to cannabis users if it were shown that the long-term ingestion of exogenous cannabinoids also leads to an imbalance in endogenous cannabinoids.

Although there is an association between cannabis use and schizophrenia, it is thought not to be the end result of prolonged cumulative exposure to cannabis, but rather an acute effect of cannabis triggering a psychotic reaction in a predisposed individual.[3,20] It has long been known that acute cannabis intoxication can produce unpleasant side effects such as feelings of anxiety and paranoia, interpersonal sensitivity and agitation, or panic reactions, particularly in naive users, or when large doses are consumed.[21] Evidence shows that high doses of cannabis may induce visual and auditory hallucinations, delusional ideas, thought disorder and hypomania, and in rare instances a transient psychotic disorder with both organic and functional features.[18] Individuals who have experienced panic attacks or psychotic reactions to cannabis are less likely to continue using,[57] but the incidence of cannabis use among people with schizophrenia is higher than that in the normal population. Most research supports the view that cannabis use among people with schizophrenia exacerbates their psychotic symptoms and leads to more relapse episodes and a poorer prognosis.[18] The mechanisms of action of cannabis in exacerbating schizophrenic symptoms are, at present, not known, although it is likely due to its interactions with the dopaminergic system.

Chronic use of cannabis is associated, however, with a high prevalence of other comorbid psychiatric disorders and a number of studies have found that various symptoms of psychological distress appear to worsen as the level of involvement with the drug progresses. A recent study of Italian army draftees with cannabinoid-positive urines found that 83 percent of those with cannabis dependence had at least one comorbid psychiatric diagnosis, compared to 46 percent of those with cannabis abuse, and 29 percent of occasional cannabis users.[58] Cannabis use has been associated with increases in schizotypal and borderline personality traits in otherwise healthy people.[61] Solowij[52] found that heavy frequency cannabis use was associated with greater psychiatric symptomatology as measured by the Symptom Checklist 90-R (SCL90-R), with significantly elevated scores on depression, anxiety, hostility, and psychoticism subscales, the Global Severity Index (GSI), and positive symptom total, and that scores remained elevated in a sample of ex-cannabis users. Other studies have not supported a causal association.[27,56]

The relationship between cannabis use, depression, anxiety, and other affective states is convoluted. Individuals often report using cannabis for therapeutic or self-medicating purposes to alleviate symptoms of depression, anxiety, and stress, to alter consciousness, and to facilitate social and sexual relations, relaxation, and sleep.[16,17,45,46,52] Some have found cannabis helpful for mania,[15] and cannabidiol, a component of cannabis, may even have antipsychotic effects (see Chapter 33). Despite this, evidence suggests that prolonged heavy use of cannabis in itself is associated with depressive states

and increased symptoms of psychological distress. Depressive symptoms have been reported to be one of the predictors of cessation of cannabis use.[5] Sometimes users can have little insight into the possibility that their cannabis use may have a causative role in their feelings of depression and anxiety, claiming only that it relieves these symptoms. Both perceptions and affective states can change dramatically after cessation of use, when the user feels that they have "come out of a fog" and have clearer, less muddy thinking.[16,52]

It is likely that early in a drug-using career cannabis is used more for its general pleasurable effects, but with frequent and prolonged use symptoms of depression, anxiety, paranoia, and insomnia may manifest, which the user attempts to alleviate with continued use of cannabis. This behavior may simply be to avoid having to cope and deal with life's problems. Cannabis users seeking treatment have reported smoking as an avoidance technique,[53] as have even short-term users with research showing that these motives for use are good indicators of problematic consequences which are also related to lifetime consumption.[50] Chronic use may also interfere with motivation, in particular with setting and achieving long-term aspirations, or even short-term goals;[27,45,53] the idea of an "amotivational syndrome" has long been touted. Evidence for such a syndrome associated with chronic cannabis use has been equivocal; chronic users may become apathetic, lethargic, withdrawn, and unmotivated, but these are probably merely symptoms of depression, cognitive impairment, and chronic intoxication.[19,21]

The use of cannabis on a daily or near-daily basis can also result in dependence (see Chapter 23) and associated withdrawal symptoms. A number of studies have reported that nervousness, anxiety, restlessness, sleep disturbances, and changes in appetite can be experienced to varying degrees.[60] A recent study has demonstrated withdrawal symptoms such as depression and anxiety after only a few days of administration of either smoked or oral THC to humans.[23] Greater numbers of cannabis users are now seeking treatment and appropriate treatments are being developed for their specific needs.[13,14,54]

One of the most frequent concerns of long-term cannabis users is that chronic use of the drug may adversely affect memory function and contribute to other lasting cognitive impairments. The long-term use of cannabis does not result in gross cognitive deficits, but there is now sufficient evidence that it leads to a more subtle and selective impairment of higher cognitive functions.[2,21,42,52] Recent research with long-term users in the unintoxicated state has demonstrated impairment of learning, organization and integration of complex information in tasks involving various mechanisms of attention, memory processes, and executive function. There is ongoing debate as to whether the deficits detected are due to the accumulation of cannabinoids (a brief drug residue effect lasting up to 24 hours), the with-

drawal from cannabinoids (since most studies have required users to abstain for a number of hours prior to testing), or whether they may indeed represent a more lasting alteration of brain function.[42] Evidence suggests that cognitive impairments are associated either with frequency of cannabis use (being maximal in heavy users), or may increase with duration of cannabis use. The latter suggests that gradual long-term changes may occur in the brain.

A series of studies by Solowij and colleagues[52] found strong and replicable associations with duration of cannabis use by using sensitive measures of brain function: event-related potentials recorded during a complex selective attention task. The results showed that the ability to focus attention and filter out complex irrelevant information was progressively impaired with the number of years of cannabis use. This deficit was also evident in a group of ex-cannabis users with a mean duration of abstinence of two years and was related to their past use of cannabis even after controlling for confounding variables. In current users only, speed of information processing was impaired with increasing frequency of use; this was interpreted as a short-term effect due to accumulated cannabinoids.

Pope and Yurgelun-Todd[44] used a select set of neuropsychological tests to demonstrate greater impairment on attentional and executive functions in heavy cannabis users than light users. This study also controlled for a variety of potentially confounding variables, such as estimated levels of premorbid cognitive functioning, and use of alcohol and other substances. Heavy cannabis users were more susceptible to interference, made more perseverative responses, had poorer recall, and showed deficient learning. This study and another by the same team[43] found some gender-specific cognitive effects of heavy cannabis use: female heavy users remembered fewer items and made more errors than female light users in a visuospatial memory task, whereas male heavy users were more impaired in attentional/interference tasks and in delayed recall than male light users.

A 17-year follow-up of chronic users[12] supported the findings that it is mainly the attentional/executive system that is impaired and that the most pronounced effects may be on the abilities to shift and/or sustain attention—functions associated with the prefrontal cortex. This study suggested an interaction with the mental deterioration that occurs with normal aging: older users performed more poorly than older nonusers on complex, short-term memory tests and on complex tasks of selective and divided attention associated with working memory, whereas no differences were found between younger users and nonusers.

The long-term cognitive effects of cannabis are quite specific and subtle, requiring sensitive measures to detect them. A recent epidemiological study with a potentially powerful longitudinal approach failed to detect any cognitive decline associated with cannabis during three study waves in 1981,

1982, and 1993-1996.[31] This was most likely due to the lack of sensitivity of the assessment instrument used. The Mini-Mental State Examination tests a restricted set of very simplistic cognitive functions used for discriminating patients with moderate to severe deficits and does not adequately measure functions such as ability to attend to relevant input, ability to solve abstract problems, and ability to retain information over prolonged time intervals. A further problem with this study was that any effect of cannabis use would have been greatly diffused by the inclusion as "heavy users" of people who may have had an isolated incident of smoking "daily or more often for over two weeks" during any one of the study wave periods but who had not used previously or since.

There is continued concern that adolescents may be at greater risk of experiencing the adverse effects of cannabis use on psyche and cognition.[20] Adolescence is a particularly vulnerable period when foundations are laid for important educational, intellectual, emotional, and maturational developments, concurrent with maturation of the CNS and reproductive system. There is evidence for impaired educational attainment among adolescents who use cannabis, and early commencement of cannabis use (e.g., prior to the age of 16) contributes to poor psychosocial adjustment[11] and impairs specific attentional functions[10] in adulthood. Two studies of cannabis-using adolescents have found evidence of short-term memory deficits, and, following abstinence of four to six weeks, a still generalized impairment of memory.[36,47] Prenatal exposure to cannabinoids can also affect cognitive development in children (see Chapter 24).

It is not clear to what extent the cognitive and psychological effects of long-term cannabis use might impact upon daily life, although cannabis users themselves complain of problems with memory, concentration, loss of motivation, paranoia, depression, dependence, and lethargy.[45,52] Schwenk[48] has argued that there is no clear causal relationship between cannabis use and job performance. The nature of the cognitive deficits as assessed by psychological testing suggests that long-term users would perform reasonably well in routine tasks of everyday life, although they may be more distractible. Difficulties are likely to be encountered in performing complex tasks that are novel or cannot be solved by automatic application of previous knowledge, or with tasks that rely heavily on a memory component or require strategic planning and multitasking. It is not yet possible to specify levels of cannabis use that are "safe," "hazardous," and "harmful" in terms of the risk of cognitive impairment or psychological harm, and indeed it may prove difficult to do so due to wide ranging individual susceptibility to such harms. The extent to which the subtle cognitive impairments may recover following cessation of use is also unknown, but research is in progress.

RELEVANCE FOR THERAPEUTIC USE OF CANNABIS

The evidence reviewed for neurotoxicity and functional deficits appears to be at odds with recent evidence that cannabinoids such as THC and cannabidiol also, intriguingly, possess neuroprotective antioxidant properties[22] (see Chapter 9). The potential for therapeutic application to a variety of neurological conditions is therefore promising and cannabidiol would be ideal for this purpose as it has no psychoactivity. Alternatively, synthetic cannabinoids, such as dexanabinol, could serve this purpose[28,39] (see also Chapter 36). Research clearly suggests other beneficial effects that cannabinoids can have on CNS function, including analgesia, reduction of intracranial pressure following head trauma, and anticonvulsant and antispasticity effects (see other chapters in this book). The current surge in research on the effects of cannabinoids on the CNS relevant to the therapeutic situation greatly exceeds in quantity any ongoing research into neurotoxicity and adverse long-term effects. Further research may show that the therapeutic benefits of cannabinoids may far outweigh any long-term adverse consequences, but there is much that remains unknown about the various interrelationships between ingested exogenous cannabinoids, the endogenous cannabinoid system, and other neuromodulator systems.

Whether THC is primarily responsible for the long-term adverse effects on the CNS, as opposed to other cannabinoids, is not certain. Most of the animal studies that provided evidence of neurotoxic effects have administered THC, but anandamide has also been shown to have very similar effects (e.g., on memory). In human usage, any number of the many other compounds in cannabis smoke could contribute to the various long-term effects on psyche and cognition. Cannabidiol appears to be relatively safe, but research should nevertheless monitor long-term outcomes and ensure that psyche and cognition are not compromised.

In general, prolonged heavy use of cannabis (daily or near-daily use) places users at greatest risk of adverse health and psychological consequences.[21] The greatest risks to psyche and cognition are the possibility of subtle impairments of memory, attention and executive function, and increased psychiatric symptomatology including depression, anxiety, and loss of motivation. Aside from acute psychotic reactions in vulnerable persons and greater severity of their symptomatology, the long-term risks for most users are not severe and their effects are relatively subtle, although individual differences in susceptibility do exist, and the extent of recovery of cognitive functioning is not yet certain.

Those considering using cannabinoids for medicinal purposes should be informed of the possible long-term effects on psyche and cognition, as users of any medication are warned of its potential side effects. It is up to the user to weigh the possible consequences against the extent of relief of their symptoms. If the nature of the symptoms is severe and the relief that

cannabinoids may bring is relatively dramatic, then the long-term effects on the CNS would be of a lesser concern, with the following caveats: (1) due to possible long-term effects on the development of the CNS in the fetus, cannabinoids should be avoided by pregnant women; (2) if relatively large doses of psychoactive cannabinoids are taken, aside from the precautions inherent during a phase of acute intoxication, there is a risk that residual effects may be experienced for hours later, and even the following day, that would affect performance of complex tasks requiring high levels of cognitive ability; and (3) until further research can elucidate mechanisms by which cannabinoids might alleviate psychiatric symptomatology, vulnerable individuals should be advised against the use of cannabinoids as they may in fact exacerbate such symptoms. If the nature of the indication for which cannabinoids were prescribed allows medical use for only a short period of time, it would be generally advisable in order to avoid or minimize adverse effects on psyche and cognition.

REFERENCES

1. Adams IB, Martin BR. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 1996; 91(11):1585-1614.

2. Block RI. Does heavy marijuana use impair human cognition and brain function? *Journal of the American Medical Association* 1996;275(7):560-561.

3. Bowers MB. Family history and early psychotogenic response to marijuana. *Journal of Clinical Psychiatry* 1998;59(4):198-199.

4. Chan GCK, Hinds TR, Impey S, Storm DR. Hippocampal neurotoxicity of Δ^9-tetrahydrocannabinol. *Journal of Neuroscience* 1998;18(14):5322-5332.

5. Chen D, Kandel DB. Predictors of cessation of marijuana use: An event history analysis. *Drug and Alcohol Dependence* 1998;50:109-121.

6. Childers SR, Breivogel CS. Cannabis and endogenous cannabinoid systems. *Drug and Alcohol Dependence* 1998;51(1-2):173-187.

7. Deadwyler SA, Heyser CJ, Hampson RE. Complete adaptation to the memory disruptive effects of delta-9-THC following 35 days of exposure. *Neuroscience Research Communications* 1995;17:9-18.

8. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;258(5090):1946-1949.

9. Diana M, Melis M, Muntoni AL, Gessa GL. Mesolimbic dopaminergic decline after cannabinoid withdrawal. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95(17):10269-10273.

10. Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, Gigerenzer G, Hoehe M. Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology* 1999;142(3):295-301.

11. Fergusson D, Horwood J. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* 1997;92(3):279-296.

12. Fletcher JM, Page JB, Francis DJ, Copeland K, Naus MJ, Davis CM, Morris R, Krauskopf D, Satz P. Cognitive correlates of long-term cannabis use in Costa Rican men. *Archives of General Psychiatry* 1996;53(11):1051-1057.

13. Grenyer BFS, Luborsky LL, Solowij N. *Treatment Manual for supportive-expressive dynamic psychotherapy: Special adaptation for treatment of cannabis (marijuana) dependence*. Technical Report 26. Sydney: National Drug and Alcohol Research Centre, 1995.

14. Grenyer BFS, Solowij N, Peters R. *Marijuana: A guide to quitting*. Sydney: National Drug and Alcohol Research Centre, 1996.

15. Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: Anecdotal evidence and the need for clinical research. *Journal of Psychoactive Drugs* 1998;30(2):171-177.

16. Gruber AJ, Pope HG Jr, Oliva P. Very long-term users of marijuana in the United States: A pilot study. *Substance Use and Misuse* 1997;32(3):249-264.

17. Gruber AJ, Pope HG Jr, Brown ME. Do patients use marijuana as an antidepressant? *Depression* 1996; 4(2):77-80.

18. Hall W. Cannabis use and psychosis. *Drug and Alcohol Review* 1998;17:433-444.

19. Hall W, Solowij N. Long-term cannabis use and mental health. *British Journal of Psychiatry* 1997;171(107-108).

20. Hall W, Solowij N. Adverse effects of cannabis. *Lancet* 1998;352(9140):1611-1616.

21. Hall W, Solowij N, Lemon J. *The health and psychological consequences of cannabis use*. National Drug Strategy Monograph Series No. 25, Canberra: Australian Government Publishing Service, 1994.

22. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Δ^9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95(14):8268-8273.

23. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 1999;141(4):385-394.

24. Heath RG, Fitzjarrell AT, Fontana CJ, Garey RE. *Cannabis sativa:* Effects on brain function and ultrastructure in rhesus monkeys. *Biological Psychiatry* 1980; 15(5):657-690.

25. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, De Costa BR, Rice KC. Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States of America,* 1990;87(5):1932-1936.

26. Jentsch JD, Verrico CD, Le D, Roth RH. Repeated exposure to Δ^9-tetrahydrocannabinol reduces prefrontal cortical dopamine metabolism in the rat. *Neuroscience Letters* 1998;246(3):169-172.

27. Kouri E, Pope HG, Yurgelun-Todd D, Gruber S. Attributes of heavy vs. occasional marijuana smokers in a college population. *Biological Psychiatry* 1995; 38(7):475-481.

28. Leker RR, Shohami E, Abramsky O, Ovadia H. Dexanabinol: A novel neuroprotective drug in experimental focal cerebral ischemia. *Journal of the Neurological Sciences* 1999;162(2):114-119.

29. Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D. Elevated endogenous cannabinoids in schizophrenia. *Neuroreport* 1999;10(8):1665-1669.

30. Lichtman AH, Martin BR. Delta-9-tetrahydrocannabinol impairs spatial memory through a cannabinoid receptor mechanism. *Psychopharmacology* 1996;126(2):125-131.

31. Lyketsos CG, Garrett E, Liang KY, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. *American Journal of Epidemiology* 1999;149(9):794-800.

32. Mallet PE, Beninger RJ. The endogenous cannabinoid receptor agonist anandamide impairs memory in rats. *Behavioural Pharmacology* 1996;7:276-284.

33. Mallet PE, Beninger RJ. The cannabinoid CB_1 receptor antagonist SR 141716A attenuates the memory impairment produced by Δ^9-tetrahydrocannabinol or anandamide. *Psychopharmacology* 1998;140(1):11-19.

34. Matsuda LA, Lolait SJ, Brownstein M, Young A, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990; 346(6284):561-564.

35. McGahan JP, Dublin AB, Sassenrath E. Long-term delta-9-tetrahydrocannabinol treatment: Computed tomography of the brains of rhesus monkeys. *American Journal of Diseases of Children* 1984;138(12):1109-1112.

36. Millsaps CL, Azrin RL, Mittenberg W. Neuropsychological effects of chronic cannabis use on the memory and intelligence of adolescents. *Journal of Child and Adolescent Substance Abuse* 1994;3:47-55.

37. Murillo-Rodriguez E, Sanchez-Alavez M, Navarro L, Martinez-Gonzalez D, Drucker-Colin R, Prospero-Garcia O. Anandamide modulates sleep and memory in rats. *Brain Research* 1998;812(1-2):270-274.

38. Musselman DL, Haden C, Caudle J, Kalin NH. Cerebrospinal fluid study of cannabinoid users and normal controls. *Journal of Psychiatric Research* 1994; 52(1):103-105.

39. Nagayama T, Sinor AD, Simon RP, Chen J, Graham SH, Jin KL, Greenberg DA. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. *Journal of Neuroscience* 1999;19(8):2987-2995.

40. Oviedo A, Glowa J, Herkenham M. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: A quantitative autoradiographic study. *Brain Research* 1993;616(1-2):293-302.

41. Pertwee RG. In vivo interactions between psychotropic cannabinoids and other drugs involving central and peripheral neurochemical mechanisms. In

Murphy L, Bartke A, eds. *Marijuana/cannabinoids: Neurobiology and neurophysiology*. Boca Raton, FL: CRC Press, 1992, pp. 165-218.

42. Pope HG, Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: The current status of research. *Drug and Alcohol Dependence* 1995;38(1):25-34.

43. Pope HG Jr, Jacobs A, Mialet JP, Yurgelun-Todd D, Gruber S. Evidence for a sex-specific residual effect of cannabis on visuospatial memory. *Psychotherapy and Psychosomatics* 1997;66(4):179-184.

44. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association* 1996; 275(7):521-527.

45. Reilly D, Didcott P, Swift W, Hall W. Long-term cannabis use: Characteristics of users in an Australian rural area. *Addiction* 1998;93(6):837-846.

46. Schafer J, Brown SA. Marijuana and cocaine effect expectancies and drug use patterns. *Journal of Consulting and Clinical Psychology* 1991;59(4):558-565.

47. Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P. Short-term memory impairment in cannabis-dependent adolescents. *American Journal of Diseases of Children* 1989;143(10):1214-1219.

48. Schwenk CR. Marijuana and job performance: Comparing the major streams of research. *Journal of Drug Issues* 1998;28:941-970.

49. Sim LJ, Hampson RE, Deadwyler SA, Childers SR. Effects of chronic treatment with delta-9-tetrahydrocannabinol on cannabinoid-stimulated [35S] GTP gamma S autoradiography in rat brain. *Journal of Neuroscience* 1996;16:8057-8066.

50. Simons J, Correia CJ, Carey KB, Borsari BE. Validating a five-factor marijuana motives measure: Relations with use, problems, and alcohol motives. *Journal of Counseling Psychology* 1998;45: 265-273.

51. Slikker W Jr, Paule MG, Ali SF, Scallet AC, Bailey JR. Behavioral, neurochemical, and neurohistological effects of chronic marijuana smoke exposure in the nonhuman primate. In Murphy L, Bartke A, eds. *Marijuana/cannabinoids: Neurobiology and neurophysiology*. Boca Raton, FL: CRC Press, 1992, pp. 219-273.

52. Solowij N. *Cannabis and cognitive functioning*. Cambridge: Cambridge University Press, 1998.

53. Solowij N, Grenyer BFS, Chesher G, Lewis J. Biopsychosocial changes associated with cessation of cannabis use: A single case study of acute and chronic cognitive effects, withdrawal and treatment. *Life Sciences* 1995;56(23-24):2127-2134.

54. Stephens RS, Roffman RA, Simpson RE. Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology* 1993;61:1110-1104.

55. Terranova JP, Storme JJ, Lafon N, Púrio A, Rinaldi-Carmona M, Le Fur G, Soubriú P. Improvement of memory in rodents by the selective CB_1 cannabinoid receptor antagonist, SR 141716. *Psychopharmacology* 1996;126(2):165-172.

56. Thomas H. Psychiatric symptoms in cannabis users. *British Journal of Psychiatry* 1993;163:141-149.

57. Thomas H. A community survey of adverse effects of cannabis use. *Drug and Alcohol Dependence* 1996;42(3):201-207.

58. Troisi A, Pasini A, Saracco M, Spalletta G. Psychiatric symptoms in male cannabis users not using other illicit drugs. *Addiction* 1998;93(4):487-492.

59. Tsou K, Brown S, Sanudopena MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB_1 receptors in the rat central nervous system. *Neuroscience* 1998;83(2):393-411.

60. Wiesbeck GA, Schuckit MA, Kalmijn JA, Tipp JE, Bucholz KK, Smith TL. An evaluation of the history of a marijuana withdrawal syndrome in a large population. *Addiction* 1996;91(10):1469-1478.

61. Williams JH, Wellman NA, Rawlins JNP. Cannabis use correlates with schizotypy in healthy people. *Addiction* 1996;91(6):869-877.

Chapter 28

Cannabis and Alcohol in Motor Vehicle Accidents

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Marie Longo

The results of science-based epidemiological research have demonstrated that alcohol has a causal role in many motor vehicle accidents (MVAs). This research has enabled the definition by legislation of a blood alcohol concentration (BAC) above which it is unlawful to drive a motor vehicle. The laws are known as the per se laws, because the legal infringement is related solely to the magnitude of the BAC. The implementation and the persistent policing of the blood alcohol laws have been remarkably successful in reducing the incidence of alcohol-related crashes.

This chapter will describe the methods employed in this research, and will emphasize the importance of the pharmacokinetics of alcohol in facilitating data collection. Research to find an equivalent means of determining the role of drugs other than alcohol in road crashes is more complicated. The reasons for this will be outlined and attempts to overcome these complications will be described, with emphasis on cannabis. The abundant literature of the psychomotor effects of cannabis in laboratory studies[8,9] lead us to anticipate a role for cannabis in motor vehicle accidents.

The epidemiological research method employed in road crash studies, referred to as "case-control," essentially examines the incidence of alcohol in two populations of drivers: those who have been involved in a crash (the "case") and those who are driving under similar conditions of road, traffic, lighting, and weather as those in the crash group, but who have not been involved in a crash (the "control").

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In a study such as this, one tests the null hypothesis. In this case, the null hypothesis is, alcohol plays no role in crashes and we will find the same proportion of drivers with alcohol in their blood in both of these groups. The results have firmly rejected the null hypothesis. Further analysis reveals that the risk of a crash increases in an exponential fashion as the BAC rises. For example, the crash risk of drivers with a BAC of 0.05, 0.1, or 0.15 gram percent is approximately 2, 7, and 26 times that of drivers with zero BAC.[4]

The drunk driving laws are therefore based on scientific evidence. However, frequently not recognized is just how much these results owe to the very special pharmacokinetic properties of alcohol. Amongst the psychoactive drugs, alcohol is unique. Two of these pharmacokinetic properties are of particular importance for the collection of research data. They are also important for the application of the per se laws. First, the rate of metabolism of alcohol is fairly constant. It is not dependent on the dose taken. The higher the dose, the longer there will be detectable levels of alcohol in the blood. It is therefore possible to make a cautious post hoc estimation of the range within which the BAC of a driver is likely to have been at the time of the crash. Frequently, there is a time delay (an hour or two) between the crash and the collection of the blood sample for analysis.

Second, alcohol is excreted to a small extent on the breath and the ratio of breath to blood concentration of alcohol is reasonably constant. Therefore it is possible to determine, with acceptable accuracy, the concentration of alcohol in the blood by analysis of a breath sample. As the blood alcohol is also correlated with alcohol concentration in the brain, so also is the degree of impairment.

Drugs other than alcohol, particularly cannabis, do not share these convenient pharmacokinetic properties (see Chapter 6). Cannabinoids are not excreted on the breath, so the collection of control cases from noncrash-involved drivers is difficult. Not surprisingly, control drivers asked to provide a blood sample very often refuse.

Because we cannot collect blood from noncrash-involved drivers for a control group, an alternative means of epidemiological study of motor vehicle accidents has been designed. Termed "culpability analysis," this method studies crashes post hoc based upon information (usually from coroners and/or police data) about the causative factors of the crash. Examination of these causative factors permits the researchers to apportion a score for each crash-involved driver to determine culpability for the crash. Although there are some differences between studies (described in Table 28.1), these scores classify each driver as "culpable" or "not culpable" for the crash. It is essential that the researchers be "blind" as to the presence or absence of any drugs in the bloodstream of the drivers when these attributions are made. The cases are then divided into groups according to the results of the blood analysis. Those drivers who had no detectable drugs in the blood constitute the

TABLE 28.1. Summary of Culpability Studies in Motor Vehicle Accidents Involving Alcohol, Cannabis, and No Drugs (As Controls)*

Culpability study	Total n	Drug-free drivers		Alcohol alone		Cannabis alone		Alcohol + Cannabis	
		n	% culpable	n	% culpable	n	% culpable	n	% culpable
Fatally injured drivers									
Warren et al.[12]	401	124	52	172	See notes	14	See notes	33	See notes
Williams et al.[13]	440	78	71	130	92 (S)	19	53 (NS)	132	95 (S)
Donelson et al.[2]	1,169	146	64	188	88[b]	4	75[b]	29	76[b]
Terhune et al.[10,c]	1,882	799	67.7	745	<0.10 BAC = 75.8 (NS) ≥0.10 BAC = 93.9 (S)	19	57.9 (NS)	37	94.6 (S)
Drummer[3]	1,045	479	70.8	262	<0.10 BAC = 74 (NS) ≥0.10 BAC = 98.1 (S)	43	60 (NS)	63	93.1 (S)
Non-fatally injured drivers									
Terhune[11,d]	497	273	34.3	74	<0.10 BAC = 53.9 (NS) ≥0.10 BAC = 73.8 (S)	17	52.9 (NS)	22	45.5 (NS)
Hunter et al.[6]	2,500	1,765	53.5	214	88.7 (S)	178	50.6 (NS)	74	93 (S)

Note: Statistical significance determined using Chi square, with the exception of Drummer[3] who used Fisher's Exact Test. S = statistically significant compared with drug-free drivers ($p < 0.05$); NS = not statistically significant compared with drug-free drivers; BAC = blood alcohol concentration (%).

*All of these studies examined other drugs in addition to alcohol and cannabis. This will explain any arithmetical differences that might appear.

[a] The culpability rate for all cannabis-positive drivers (no breakdown between those with and those without alcohol) was 90%. This was 1.7 times greater than the culpability rate for drug-free drivers. However, 69% of cannabis-positive drivers also tested positive for alcohol. No information provided on statistical significance for any of the between-group comparisons. No analysis for cannabis alone.

[b] The number of drivers who tested positive for cannabis alone was too small for any meaningful comparison with the drug-free drivers. No information provided on statistical significance for alcohol alone, cannabis alone, or for alcohol + cannabis.

[c] Note that culpable drivers included those who were "fully culpable" and those who were "culpable/contributory." Authors used five categories of culpability.

[d] When including drivers who were "culpable/contributory" for both drug-free and cannabis-alone groups the culpability rate was significantly higher in the cannabis group than that of drug-free drivers (76.4% versus 42.5%, $p<0.05$).

control group. The fact that these controls themselves had been involved in a crash sharply distinguishes this study from the noncrash-involved control group of drivers in the case-control method.

For the culpability analysis, the null hypothesis is, drugs play no role in crashes and the distribution of culpable drivers is not significantly different between the "drug positive" and the "no drug" groups.

HOW CANNABIS PHARMACOKINETICS PRESENTS MORE PROBLEMS

Unfortunately, some of the research results to date have overlooked the problems presented by the peculiar pharmacokinetics of cannabis.

Alcohol kinetics present sufficient information to provide an acceptable correlation between blood (or breath) alcohol and probability of accident causality. The detection and quantification of alcohol in the blood of a driver is sufficient evidence for the determination of impairment.

Cannabis pharmacokinetics are not so simple (see Chapter 6). Two major properties must be mentioned (both of which refer to the ingestion of cannabis by smoking, the most common means of administration). These properties can affect the interpretation of data in the culpability analysis studies, and include

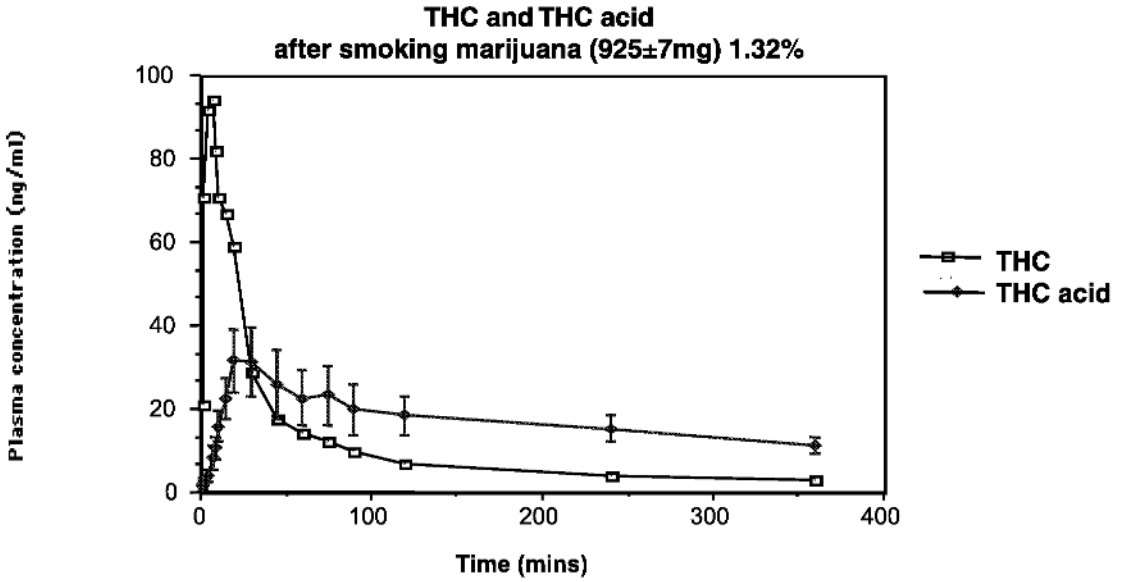
1. the extremely rapid rate of removal from the bloodstream of THC (Δ^9-tetrahydrocannabinol) after smoking; and
2. the accumulation in the blood of the major psychologically inactive metabolite THC acid (11-nor-9-carboxy-THC) and, to a lesser extent, of the THC itself. Such accumulation is apparent if frequency of use is greater than once per week.

These properties are graphically illustrated in Figure 28.1.

Removal from the Bloodstream

From Figure 28.1 it can be seen that before smoking (at time zero in the graph) the blood of these volunteers is devoid of both THC and metabolite. Very soon after smoking begins, the concentration of THC rises extremely rapidly, reaches a peak, and rapidly declines. Indeed, the decline usually begins before smoking has finished. One notes also the appearance of the metabolite of THC after the smoking of the marijuana cigarette. Apart from the first 15 to 20 minutes after smoking, the concentration of metabolite exceeds that of the parent THC and it stays in the plasma longer. Should smoking begin again within a few hours or even three to five days, the accumulation of the newly administered THC will be additive to that already present

FIGURE 28.1. The Blood Concentration of THC (Squares) and Its Inactive Metabolite, Carboxy THC (THC Acid, Diamonds) After the Smoking of a Marijuana Cigarette



Source: Drawn from data from Perez-Reyes M, Di Guiseppi S, Davis K, Schindler V, Cook C. Comparison of effects of marijuana cigarettes of three different potencies. *Clinical Pharmacology and Therapeutics* 1982;31(5):617-624.

and the generation of metabolite from this newly administered THC will also be additive to that already in the circulation.

The very rapid removal of THC from the blood means that there is a poor correlation between blood concentration of THC and that in the brain (unlike alcohol). Because of these pharmacokinetic properties, it is at present not possible to determine the degree of impairment of a driver from blood analysis data. Therefore, the major task for the interpreter of blood data is to make a judgment whether or not the cannabis use by the driver has been recent and whether the driver was under the influence (i.e., intoxicated or "stoned") at the time of the crash. In order to do this, analytical results must include detection and quantification of THC and of the major metabolite THC acid. The assumption of recent use can only be made when there is detectable THC in the blood sample. The inclusion of cases with only the metabolite, and therefore no evidence for recent use to imply possible impairment, will falsify the analysis.

On the other hand, the rapid rate of change in concentration of THC between the time of the crash and the collection of the blood sample may lead to a false-negative classification. If there is a long interval, the concentration

of THC may fall from being at a detectable level at the time of the crash to an undetectable concentration at the time the blood sample is taken. It is important, therefore, that this interval always be reported for all cases. It is desirable that a "standard limit" be agreed upon for future studies. Perhaps a maximum of four hours might be considered.

Accumulation

The second pharmacokinetic property that may influence the ability to determine accurately the time of consumption of cannabis concerns the cumulative properties of both THC and its acid metabolite.

Due to these cumulative properties, regular users of the drug who present a blood sample containing both THC and the metabolite pose a problem of interpretation; a problem that requires more research to resolve. Samples with a very high ratio of metabolite to THC possibly identify a regular user of the drug who may or may not be intoxicated at the time of the collection of the blood sample. This is a problem that at present is of concern only for individual cases before the courts. It may, however, confound data interpretation for epidemiological studies. It would be desirable, therefore, to perform a separate analysis for those cases where a frequent user is suspected (by the high metabolite/THC ratio) to determine if the culpability score differs from those with a lower metabolite to THC ratio. The confounding variable is whether the frequent user was or was not intoxicated at the time of the crash. An extreme example of the accumulation of the parent molecule is reported by Agurell et al.[1] A very heavy smoker was found to have a blood concentration of the parent molecule (THC) of 10 ng/ml in a blood sample taken more than 24 hours after his last smoke.

RESULTS OF CULPABILITY STUDIES

To date (September 1999), seven studies using culpability analysis have been reported, involving a total of 7,934 drivers. Alcohol was detected as the only drug in 1,785 drivers, and together with cannabis in 390 drivers. Cannabis was detected in 684 drivers, and in 294 of these it was the only drug detected.

The results of these studies are outlined in Table 28.1. This table presents the data upon which the culpability analysis was made. These data describe cannabis as being the detection of THC metabolites with or without THC. The prominent features to be noted here include the significant and dominant role of alcohol in crashes. One also notes the nonsignificant role of cannabis.

Comments and Cautions About the Interpretation of These Results

Before accepting these results we should consider the comments made about THC pharmacokinetics. Pertinent to the interpretation of these results are the differences in methodology between the studies described in Table 28.1. These differences are outlined in Table 28.2.

The seven studies are from six different research groups. Although having much in common methodologically, they do differ in some technicalities. Of the seven culpability studies, five involved fatally injured drivers, and two, nonfatally injured drivers. The methods for determination of culpability differed slightly between studies, depending essentially upon the data employed and the objectivity of the assessment.

The time interval between the crash and the collection of the blood sample was not reported in two of the studies, but in the others most deaths occurred within two to four hours. A delay in the time between the crash and the collection of blood might mean that some THC-positive cases were missed.

The most important factor in analytical data is the quantification of THC. In Table 28.1, the data are presented as in the original publication upon which the culpability scores were calculated. Table 28.2 reports only the analysis of blood samples. In three studies[3,6,12] many cases were included in the culpability analysis in which the metabolite only was detected, thus casting some doubt on the reported results.

The data from Hunter et al.[6] have been reanalyzed using only the 65 cannabinoid cases for which THC had been detected and of these, 50 were in the group for which cannabis was the only drug. This reanalysis reported by Longo et al.[7] found that the culpability index of the cannabis-only drivers was not significantly different from those of the "control" drug-free group. This finding is of particular importance because by removing the cases for which THC had not been detected, they have confirmed their earlier results.

These results also correspond with the four other studies in Table 28.2[2,10,11,13] for which the culpability analysis was performed on a total of 279 cases, in all of which THC had been detected. Of these, THC appeared as the only drug in 59 cases. In each study, the culpability of the THC group was not significantly different from that of the "no drug" group.

The Interaction Between Cannabis and Alcohol

Several of the studies[2,5,6,9,12] have addressed the issue of the interaction between alcohol and cannabis. In all cases the culpability rate of drivers was not significantly different between those in the alcohol alone group and those with alcohol plus cannabis. This suggests that the increased crash risk

TABLE 28.2. Methodological Differences Between Culpability Analysis Studies

Culpability study	Cannabinoids detected (alone or in combination with alcohol)	Time delay between crash and blood sample collection
Fatally injured drivers		
Warren et al. [12]	47 drivers tested positive for cannabinoids: 14 with THC, 2 of which were in the cannabis-only group. Radioimmunoassay screen only.	Drivers were dead on arrival at hospital, or died shortly thereafter. No information on time delay.
Williams et al. [13]	151 drivers tested positive for cannabinoids: 151 with THC, 19 of which were in the cannabis-only group. Radioimmunoassay screen with GC/MS confirmation.	Drivers died on impact or within two hours of the crash. No information on time delay.
Donelson et al. [2*]	33 drivers tested positive for cannabinoids: 33 with THC, 4 of which were in the cannabis-only group.	Drivers died within one hour of crash. No information on time delay.
Terhune et al. [10]	56 drivers tested positive for cannabinoids: 56 with THC, 19 of which were in the cannabis-only group. Radioimmunoassay screen with GC/MS confirmation.	The majority of drivers (94%) died within two hours of the crash and 6% died within four hours. Authors concluded survival time had little impact on drug prevalence rates. Distribution of time delay for drivers who died within two hours of the crash: 41.2% < 8 hours, 13% 8 to12 hours, 25.8% 12 to 24 hours, 20% over 24 hours. Authors suggested time delay may have affected drug prevalence rates (and drug concentrations) but did not attempt to calculate concentrations at time of crash.
Drummer [3]	106 drivers tested positive for cannabinoids: 2 with THC; both were in the cannabis-only group. Radioimmunoassay screen with GC/MS confirmation.	No information on selection criteria for drivers, or on time delay.

Nonfatally injured drivers

Terhune [11]	39 drivers tested positive for cannabinoids: 39 with THC, 17 of which were in the cannabis-only group. Radioimmunoassay screen with GC/MS confirmation.	Crash occurred less than four hours before arrival at hospital. Distribution of time delay: 20.3% < 1 hour, 41.9% 1 to 2 hours, 31.2% > 2 hours, 6.2% unknown. Authors found no differences in the THC distribution of the earlier and later samples. Concluded that at the time of blood sample collection the THC concentrations of most drivers were decreasing at a low rate.
Hunter et al. [6]	252 drivers tested positive for cannabinoids: 65 with THC; 50 of these were in the cannabis-only group. Radioimmunoassay screen with GC/MS confirmation.	Distribution of time delay: 15.1% < 1 hour, 39.4% 1 to 2 hours, 20.3% 2 to 3 hours, 9.8% 3 to 4 hours, 5.6% 4 to 5 hours, 9.9% > 5 hours.

Note: Screening methods alone are not reliable. Further definitive testing is essential for identification and quantification of drug(s).

* The original data set was 1,169 drivers; funding problems permitted the analysis on only 367.

reported for alcohol plus cannabis was due to the alcohol effect which clouded any evidence for an interaction between these drugs.

When this comparison is broken down according to blood alcohol concentration, the nonsignificance remains, even in the lower BAC ranges of <0.08 and <0.05 percent. In a reanalysis of original data in a study by Hunter et al.,[6] Longo et al.,[7] when they included only those cases with detectable THC in the blood sample, found the same nonsignificant comparison between alcohol and alcohol plus THC.

CONCLUSION

Using the culpability analysis method, the dominant role of alcohol in motor vehicle accidents is clearly demonstrated, confirming the results with the case-control method. Indeed, in three of the studies outlined in Table 28.1 the concentration-dependence of alcohol was exhibited. At BAC ≥0.10 the culpability ratios were significant, whereas BAC <0.10 did not achieve significance.

The results to date of crash culpability studies have failed to demonstrate that drivers with cannabinoids in the blood are significantly more likely than drug-free drivers to be culpable in road crashes. These results can be criticized on the grounds that some studies included cases in which metabolites only were detected in the blood samples. However, when these cases were eliminated and the data for cases in which THC was the only drug present were analyzed,[6] the culpability ratio was found to be not significantly different from the no-drug group.

There was no evidence to suggest an additive interaction between alcohol and cannabis.

Problems with the method of culpability analysis exist, the greatest of which are associated with the pharmacokinetics of cannabinoids. The culpability analysis results reported to date involve a very small sample of cannabis-only drivers, and an even smaller number for which THC data are available.

At the present time, the evidence to suggest an involvement of cannabis in road crashes is scientifically unproven. We must await results of more studies for clarification and confirmation. However, the authors' attention has been drawn to a study[3] of Australian drivers killed in motor vehicle accidents, of whom 10 were positive for THC as the only drug present. Eight of these were culpable and two nonculpable. The mean blood concentration of THC in the culpable drivers was 15 ± 14 ng/ml and that of the nonculpable drivers was 3.5 ng/ml. Drummer (personal communication) indicates that more data, yet unpublished, further support this finding of a higher involvement of THC as a causal factor in motor vehicle accidents.

REFERENCES

1. Agurell S, Halldin M, Lindgren J-E, Ohlsson A, Widman M, Gillespie H, Hollister L. Pharmacokinetics and metabolism of delta-1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacological Reviews* 1986; 38(1):21-43.

2. Donelson A, Haas G, Walsh P. *The etiology of fatal traffic accidents involving alcohol and cannabis*. Ottawa: The Traffic Injury Research Foundation of Canada, 1986.

3. Drummer O. *Drugs and drivers killed in Australian road traffic accidents. The use of responsibility analysis to investigate the contribution of drugs to fatal accidents*. Victorian Institute of Forensic Pathology. Monash University, 1994.

4. Drummer OH, Gerostamoulos J, Batziris H. *Involvement of drugs in accident causation*. Australia: Federal Office of Road Safety Meeting, September, 1998.

5. Evans L. *Traffic safety and the driver*. New York: Van Nostrand Reinhold, 1991.

6. Hunter C, Lokan R, Longo M, White J, White M. *The prevalence and role of alcohol, cannabinoids, benzodiazepines and stimulants in nonfatal crashes*. Adelaide, South Australia: Forensic Science, Department for Administrative and Information Services, 1998.

7. Longo MC, Hunter CE, Lokan RJ, White JM, White MA. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability. Part II: The relationship between drug prevalence and drug concentration, and driver culpability. *Accident Analysis and Prevention* 2000;32(5):623-632.

8. Moskowitz H. Marihuana and driving. *Accident Analysis and Prevention* 1985;17:323-345.

9. Perez-Reyes M, Di Guiseppi S, Davis K, Schindler V, Cook C. Comparison of effects of marijuana cigarettes of three different potencies. *Clinical Pharmacology and Therapeutics* 1982;31(5):617-624.

10. Terhune K, Ippolito C, Hendricks D, Michalovic J, Bogema S, Santinga P, Blonberg R, Preusser D. *The incidence and role of drugs in fatally injured drivers*. Washington, DC: U.S. Department of Transportation National Highway Traffic Safety Administration, 1992.

11. Terhune K. *The role of alcohol, marijuana and other drugs in the accidents of injured drivers*. Technical report prepared for the U.S. Department of Transportation, Contract No DOT-HS-5-01179, Buffalo, NY: Calspan Field Services Inc, 1982.

12. Warren R, Simpson H, Hilchie J, Cimbura G, Lukas D, Bennett R. Drugs detected in fatally injured drivers in the Province of Ontario. In Goldberg L, ed. *Proceedings of the 8th International Conference on Alcohol, Drugs and Traffic Safety*. Stockholm: Almqvist and Wiksell International, 1981.

13. Williams A, Peat M, Crouch D, Wells J, Finkle B. Drugs in fatally injured young male drivers. *Public Health Reports* 1985;100(1):19-25.

Chapter 29

Respiratory Risks from Marijuana Smoking

Donald P. Tashkin

INTRODUCTION

The smoke contents of marijuana are at least qualitatively similar to those of tobacco, with the major exception that marijuana smoke contains Δ^9-tetrahydrocannabinol (Δ^9-THC) and approximately 60 additional cannabinoid compounds not found in tobacco, and that tobacco contains nicotine that is absent from marijuana.[13] Many of the ingredients that are common to marijuana and tobacco smoke are known to be toxic to respiratory tissue. These toxic components include hydrocyanic acid, oxides of nitrogen, acrolein, reactive aldehydes, and several known carcinogens. It is therefore reasonable to expect that repeated inhalation of the noxious components in cannabis smoke may have long-term adverse effects on the lung similar to those that have been observed in regular tobacco smokers.

CHRONIC BRONCHITIS AND EMPHYSEMA

Clinical studies conducted in the 1970s led to conflicting conclusions regarding the impact of regular marijuana use on the lung.

Subsequent large-scale, controlled studies carried out in the 1980s revealed that regular use of cannabis was associated with both chronic (i.e., present on most days for ≥3 months for ≥2 consecutive years) and acute respiratory symptoms. For example, in a convenience sample recruited from the greater Los Angeles area that included 144 daily smokers of marijuana (MS) only, 135 smokers of both marijuana and tobacco (MTS), 70 smokers of tobacco (TS) only, and 97 nonsmokers (NS), Tashkin and colleagues[28] found that MS, compared to NS, had a significantly higher prevalence ($P < 0.05$; x^2) of chronic cough (18 percent versus 0 percent, respectively), chronic sputum production (20 percent versus 0 percent),

wheeze (25 percent versus 3.5 percent), and episodes of acute bronchitis (13 percent versus 2 percent), while the prevalence of symptoms of chronic and acute bronchitis were not significantly different between MS and TS. No additive effects of marijuana and tobacco were noted, however. Somewhat similar findings were reported by Bloom et al.;[4] in contrast to the Los Angeles study, however, an additive effect of marijuana and tobacco on chronic respiratory symptoms was noted. More recently, the respiratory effects of cannabis dependence were assessed in 943 young adults who were 21 years of age born in Dunedin, New Zealand, from a birth cohort of whom 91 subjects (9.7 percent) were cannabis-dependent.[31] After controlling for tobacco use, the following respiratory symptoms were significantly increased in cannabis-dependent subjects compared to nontobacco smokers: early morning sputum production (144 percent); wheezing apart from colds (61 percent); exertional breathlessness (65 percent); and nighttime awakenings with chest tightness (72 percent). Moreover, the prevalence of respiratory symptoms in cannabis-dependent subjects was similar to that in smokers of ≤ 10 cigarettes/day. Thus, findings from at least three controlled studies indicate that regular use of marijuana is associated with both chronic and acute bronchitis.

Chronic bronchitis is defined by the presence of *symptoms* of mucus hypersecretion, namely chronic cough and expectoration of sputum. Chronic bronchitis is associated with histopathologic alterations involving the walls of the bronchi, including smoking-related damage to the normal ciliated epithelium that lines the airways, its replacement by surface nonciliated cells, including mucus-secreting "goblet" cells, and hypertrophy of subepithelial mucus glands. Bronchial biopsies obtained from a convenience sample of 40 MS, 31 TS, 44 MTS, and 53 NS have shown a significantly higher frequency of histopathologic alterations associated with chronic bronchitis in both MS and TS compared to NS, with no significant differences between MS and TS, and evidence of an additive effect of marijuana and tobacco on bronchial epithelial histopathology.[12]

The presence of symptoms and bronchial histopathologic features of chronic bronchitis do not necessarily imply the presence of airway *obstruction,* which is an essential feature of chronic *obstructive* pulmonary disease (COPD). COPD consists of chronic *obstructive* bronchitis and/or pulmonary emphysema in varying proportions, with either one or the other often predominating. The hallmark of COPD is functional evidence of progressive airways narrowing, which is most readily detected by an accelerated decline in the forced expiratory volume in one sec (FEV_1).[11] In the Tucson study, current smokers of marijuana aged 15 to 40 years (mean 27 years) of age showed significantly lower values for the ratio of FEV_1 to forced vital capacity (FVC) than nonsmokers, and even numerically lower values for these measures than current smokers of tobacco alone, although the mean

values for these indices were still within statistically normal limits based on population-derived prediction equations.[4] A six-year follow-up study of the Tucson cohort revealed a significant reduction in FEV_1, and FEV_1/FVC in relation to previous use of marijuana (≥1 year after marijuana smoking was reported), but surprisingly not in current users.[24] It is not clear from these results whether continuing marijuana use is associated with a progressive decline in lung function. In a recent study from New Zealand, 36 percent of 21-year-old cannabis-dependent subjects (only a third of whom had been cannabis-dependent at age 18) were found to have a reduced FEV_1/FVC ratio (<80 percent), compared to only 20 percent for nonsmokers from the same birth cohort, a difference that was marginally signficant ($p = 0.04$).[31] These findings suggest that only a relatively short duration of heavy cannabis use may lead to early obstructive ventilatory impairment in young individuals, although it is not clear from this study whether the potentially confounding effect of concomitant tobacco use was adequately controlled for.

In contrast to the above findings, the Los Angeles study of 124 MS, 56 TS, 113 MTS, and 92 NS who underwent an extensive battery of pulmonary function tests failed to find any association between heavy, habitual use of marijuana (mean of >3 joints/day for >15 yrs) and abnormalities in even the most sensitive measures of early functional impairment in COPD.[28] Moreover, mean values for none of these measures was different from the average values observed in nonsmokers.

In view of the conflicting evidence from cross-sectional studies concerning an association between marijuana use and lung function abnormality, Tashkin and colleagues[29] sought to evaluate further whether habitual marijuana use might lead to progressive declines in lung function over time as occurs in COPD. Although tobacco smoking was associated with a significant age-related decline in FEV_1 compared to the change in NS, no effect of even heavy marijuana smoking on the rate of decline in FEV_1 was observed, nor was an additive effect of marijuana and tobacco noted. These findings do not suggest an association between regular marijuana smoking and COPD. This conclusion is supported by experimental animal studies in which rats were exposed to progressively increasing doses of marijuana or tobacco smoke for six months.[14] Postmortem examination of the lungs of the tobacco-exposed rats showed morphometric and physiologic evidence of emphysema (loss of lung parenchyma and decrease in lung elasticity), while the rats exposed to a similar quantity of marijuana smoke for the same duration showed no detectable morphologic or physiologic abnormalities compared to unexposed control animals.

RESPIRATORY CANCER

A number of lines of evidence support the view that marijuana use may be a significant risk factor for the development of respiratory cancer, as outlined.

1. The smoke contents of marijuana include several known carcinogens, including vinyl chlorides, phenols, nitrosamines, reactive oxygen species, and a variety of polycylic aromatic hydrocarbons (PAHs).[13,21,8] Benz[α]anthracene and benzo[α]pyrene, two highly procarcinogenic PAHs, are present in 25 to 75 percent higher concentrations in the tar from marijuana compared to tobacco.[13,15]

2. The deposition of PAHs in the tar phase of marijuana smoke is amplified approximately four times by the two- to threefold higher tar yield of unfiltered marijuana cigarettes compared to filter-tipped, more tightly packed tobacco cigarettes, and by the fourfold longer breathholding time for marijuana than tobacco smoke, which results in a 40 percent greater deposition of marijuana tar in the respiratory tract.[34]

3. THC has been shown to activate the transcription of the cytochrome P4501A1 (CYP1A1) gene to increase production of CYP1A1, the enzyme that is primarily responsible for converting PAHs to carcinogens in the lung.[22] Although PAHs themselves have long been known to induce CYP1A1, a process that is believed to be an important step in the development of tobacco-related cancers, the additive effect of THC on this enzyme-induction process has not been appreciated until recently.

4. In vitro studies using the Ames *Salmonella*/microsome test have shown that marijuana tar induces the same numbers of mutations as those produced by tobacco tar, confirming that constituents in marijuana can cause genetic mutations that could predispose to malignancy.[5,33]

5. When tar from marijuana cigarettes was painted onto the skin of mice it led to the development of metaplastic and neoplastic lesions.[7]

6. Hamster lung explants that were repeatedly exposed to either marijuana or tobacco smoke for two years developed disturbances in cell morphology, proliferation, and genetic equilibrium, leading to accelerated malignant transformation. Moreover, these changes were most impressive in the marijuana-exposed explants.[16]

7. Bronchial wall biopsies in 40 smokers of marijuana only (MS) revealed extensive hyperplastic, metaplastic, and dysplastic changes in the MS which are believed to be precursors of bronchogenic carcinoma.[12] Moreover, immunohistopathologic studies in bronchial biopsies of these subjects showed overexpression in the biopsies from MS of surrogate endpoint markers that are linked to an increased risk of lung cancer, including Ki-67 (a marker of cell proliferation) and epidermal growth factor receptor (EGFR).[3]

8. Increasing evidence points to THC as an immune modulator, with in vitro and animal studies suggesting a general immunosuppressive effect on

macrophages, natural killer cells, and T lymphocytes (see Chapter 25). Increasing evidence suggests that THC may exert its immunosuppressive effects by inhibiting the ability of lymphocytes to produce immunostimulatory Th-1 cytokines, such as interleukin-2 (IL-2) and interferon gamma (IFN-γ), while promoting their production of immunoinhibitory Th-2 cytokines, such as interleukin-10 (IL-10) and interleukin-4 (IL-4) (see Chapter 10). One potential consequence of this immunosuppressive effect of THC is impairment in the host's ability to develop antitumor immunity, thus contributing to tumor cell growth, as recently demonstrated in two murine models of lung cancer.[36] Administration of THC significantly enhanced[36] tumor growth in these animal models, an effect that was blocked by a selective antagonist against the cannabinoid-2 (CB_2) receptor. These findings suggest that THC may inhibit immune-mediated eradication of tumor cells in mouse models of lung cancer by a cytokine-dependent, cannabinoid-receptor-mediated mechanism. In correlative in vitro studies using mixed human leukocytes (purified human T cells and allogeneic antigen-presenting dendritic cells) incubated in the presence and absence of THC, THC produced a dose-dependent suppression of T cell proliferation and simultaneous inhibition of INF-γ release,[23] impairing antitumor immunity as well. Finally, alveolar macrophages, key effector cells in the lung's immune defense system, when harvested from habitual marijuana smokers and thus chronically exposed in vivo to THC and other marijuana smoke components, have been shown to be impaired in their ability to kill tumor cell targets, compared to macrophages obtained from nonsmokers and even tobacco smokers.[1]

9. Although respiratory cancer is rare in young individuals, several small case series have shown that an unusually high proportion of young individuals (under age 40 to 45 years) who develop either upper respiratory (head and neck) cancer[9,30] or lung cancer[27] have been marijuana smokers. For example, out of a total pool of 887 patients of all ages with respiratory cancer, Taylor[30] identified ten patients under age 40 years with either upper respiratory tract cancer (N = 8) or lung cancer (N = 2). Interestingly, of these ten patients, seven were heavy or regular users of marijuana and one additional patient probably used marijuana. Moreover, not all of these patients had other identified risk factors for cancer (e.g., heavy tobacco smoking, alcohol use). Similar results were obtained in a study by Sridhar et al.[27], in which *all* 13 patients under age 45 years in whom lung cancer was diagnosed at a single oncology clinic had a history of marijuana smoking. Findings from these case series suggest that marijuana smoking may be an important risk factor for the unusual development of respiratory cancer in young individuals. However, the true effect of marjiuana smoking on the risk of respiratory cancer cannot be estimated without an appropriate control group. Well-designed, adequately powered epidemiologic studies are therefore required

to obtain a valid estimate of the role of marijuana smoking in cancer development.

10. Two epidemiologic studies, one a cohort study and the other a case-control study, have examined the possible association between marijuana use and cancer. In the cohort study, between 1979 and 1985, 65,000 Northern California Kaiser Permanente health plan members 15 to 49 years of age completed health screening questionnaires that included limited information of marijuana use.[26] Follow-up of this cohort until 1993 failed to reveal any effects of lifetime or current marijuana use on the risk for development of new tobacco-related cancers.[26] The major limitations of this study included (1) the relatively young age of the cohort at follow-up (mean age 43 years), which may have precluded detection of sufficient numbers of cancers (which are more likely to occur in older individuals) to demonstrate an association with marijuana use, and (2) lack of sufficient numbers of heavy and/or long-term marijuana smokers to observe an effect.

In a case-control study of 173 patients with newly diagnosed squamous cell carcinoma of the head and neck, and 176 cancer-free age- and gender-matched control subjects evaluated at Memorial Sloan-Kettering Cancer Center (New York) between 1992 and 1994, marijuana use was associated with a significantly increased risk of head and neck cancer (odds ratio (OR) comparing ever with never users, 2.6; 95 percent confidence interval (CI), 1.1 to 6.6) after controlling for age, gender, race, education, alcohol use, and cigarette smoking.[35] Moreover, dose-response relationships were found and the effects of marijuana use and cigarette smoking were more than multiplicative.

Taken together, therefore, several lines of evidence from a variety of sources—biochemical, cellular, molecular, genetic, immunologic, clinical and epidemiologic—all suggest that marijuana has carcinogenic potential and may be an important risk factor for the development of respiratory cancer.

RESPIRATORY TRACT INFECTION

Extensive alterations in tracheobronchial epithelial histopathology have been observed in bronchial biopsies from smokers of marijuana alone or with tobacco, including loss of ciliated epithelium and replacement by mucus-secreting surface epithelial cells.[12] These alterations imply an impairment of the mucociliary clearance function of the airways, which represents the lung's first line of defense against infection, thereby predisposing to infection of the lower respiratory tract. Alveolar macophages are the key effector cells in the lung's immune defense system and represent the lung's second line of defense against infection. Marijuana smoking has been shown to result in alterations in the functional activity of these important cells, including a significant impairment in microbicidal activity for fungi and for pathogenic bacteria.[1,25] Interestingly, macrophages from tobacco-

only smokers, unlike those from marijuana-only smokers, are not impaired in their ability to kill *Staphylococcus aureus*.[1] Recent data suggest that these microbicidal defects may be due to THC-related impairment in production of reactive nitrogen intermediates (important effector molecules in bacterial killing) as a result of an inhibition of production of inducible nitric oxide synthase (NOS) by marijuana in the course of infection.[2] This inhibition appears to be due to a THC-related impairment in production of key proinflammatory cytokines (e.g., INFγ and GM-CSF) that mediate the induction of NOS. In further support of this hypothesis are other data indicating an inhibition of lipopolysaccharide-stimulated production of TNF-α, IL-6, and GM-CSF by alveolar macrophages harvested from marijuana smokers but not from tobacco smokers.[1] The clinical implications of these findings are that marijuana smoking may breach the lung's second line of defense against infection due to impairment in the critical antimicrobial function of alveolar macrophages.

When combined with the marijuana-related impairment in mucociliary function (the lung's *first* line of defense), the additional impairment in alveolar macrophage function (the lung's *second* line of defense) implies the strong possibility that marijuana smoking may predispose to pulmonary infection, especially in patients whose immune defenses are already compromised by HIV infection and/or cancer and cancer chemotherapy. This possibility is supported by the results of a few older epidemiologic studies that have shown marijuana to be a significant independent risk factor for the development of opportunistic pulmonary infection in HIV-positive individuals.[6,20,32] The possible role of marijuana smoking in the predisposition of HIV-positive patients to pneumonia requires further investigation by more rigorous epidemiologic studies in view of, on the one hand, the growing interest in medicinal marijuana, and, on the other hand, the potentially serious consequences of pulmonary infection, including a *high likelihood of mortality,* for patients who are already severely immunocompromised by AIDS or malignancy.

Another source of marijuana-related pulmonary infection is contamination of marijuana (see Chapter 30) with *Aspergillus fumigatus,*[17] potentially resulting in invasive Aspergillus pneumonia, as reported in immunocompromised patients who smoked marijuana, or in allergic bronchopulmonary aspergillosis, as also previously reported. Marijuana has also been shown to be contaminated with potentially pathogenic gram-negative bacteria.

OTHER POTENTIAL RESPIRATORY COMPLICATIONS OF MARIJUANA SMOKING

Isolated cases of spontaneous pneumothorax and/or pneumomediastinum have been associated in temporal association with marijuana use.[10,18,19] The

mechanism of these events is believed to be related to barotrauma to the lung as a result of the increased intrathoracic pressure that results when a Valsalva maneuver is performed against a closed glottis after deep inhalation of marijuana smoke in an effort to "pressurize" the smoke within the lung to enhance absorption of THC. A "tension pneumothorax" can also result if the air leak persists and pressure builds up in the pleural space or mediastinum, potentially leading to impairment in venous blood return to the heart and cardiovascular collapse. The clinical implications with regard to medicinal marijuana in certain patient populations is that patients with already compromised lung function (e.g., due to possible effects of HIV-related pulmonary infection or pulmonary involvement by cancer) can ill afford another insult to the lung from marijuana-related barotrauma that aggravates any pre-existing impairment in lung function. Furthermore, some of the pulmonary complications of AIDS (e.g., *Pneumocystis carinii* pneumonia) may also lead to pneumothorax, thus potentially causing diagnostic confusion in patients who smoke marijuana for medicinal purposes.

MONITORING FOR RESPIRATORY AND INFECTIOUS COMPLICATIONS OF MEDICINAL MARIJUANA

The following approach to monitoring for respiratory and infectious complications of medicinal marijuana should be considered:

- Marijuana cigarettes prescribed for medicinal purposes should be sterilized (e.g., irradiated) to eliminate bacterial contamination (although the impact of standard sterilization procedures on the presence of *Aspergillus* spores is unclear).
- Surveillance cultures of marijuana cigarettes earmarked for medicinal use should be performed periodically as an additional precaution to guard against bacterial and/or fungal contamination.
- Patient education: the patient should be educated to avoid the Valsalva maneuver during smoking and to promptly report to the physician any of the following symptoms or signs suggesting infection or barotrauma: fever, change in cough and/or sputum, hemoptysis, dyspnea, or chest pain.
- Patients receiving medicinal marijuana, especially those with HIV infection or other disorders associated with immune deficiency, should be monitored carefully through frequent follow-up visits.

- No obvious benefit accrues from *routine* surveillance diagnostic procedures, such as pulmonary function tests, arterial blood gases, chest radiographs or sputum examinations. Rather, specific diagnostic procedures (e.g., chest X-ray, sputum examination) should be driven by *clinical suspicion* of particular complications (e.g., pneumonia).

REFERENCES

1. Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American Journal of Respiratory and Critical Care Medicine* 1997;156(5): 1606-1613.

2. Baldwin GC, Tashkin DP, Choi R, Shay AH, Dubinett SM, Roth MD. *Antimicrobial and tumoricidal activity of alveolar macrophages from substance abusers*. Presented at the 1999 FASEB Summer Research Conference on "Pulmonary Pathophysiologic and Immune Consequences of Smoked Substance Abuse," Copper Mountain, CO, July 1999.

3. Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. Similar molecular alterations in bronchial epithellium are observed in habitual smokers of marijuana, cocaine and/or tobacco. *Journal of the National Cancer Institute* 1998; 90:1198-1204.

4. Bloom JW, Kaltenborn WT, Paoletti P, Camilli A, Lebowitz MD. Respiratory effects of nontobacco cigarettes. *British Medical Journal* 1987;295(6612):1516-1518.

5. Busch FW, Seid DA, Wei ET. Mutagenic activity of marihuana smoke condensates. *Cancer Letters* 1979;6(6):319-324.

6. Caiaffa WT, Vlahov D, Graham NM. Drug smoking. *Pneumocystis carinii* pneumonia, and immunosuppresion increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive infection drug users. *American Review of Respiratory Disease* 1994;150(6 Pt. 1):1493-1498.

7. Cottrell JS, Sohn SS, Vogel WH. Toxic effects of marihuana tar on mouse skin. *Archives of Environmental Health* 1973;26(5):277-278.

8. Dinissenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benz[α]pyrene adducts at lung cancer mutational hotspots in P53. *Science* 1996; 274(5286):430-432.

9. Donald PJ. Advanced malignancy in the young marijuana smoker. *Advances in Experimental Medicine and Biology* 1991;288:33-56.

10. Feldman AL, Sullivan JT, Passero MA, Lewis DC. Pneumothorax in polysubstance-abusing marijuana and tobacco smokers: Three cases. *Journal of Substance Abuse* 1993;5(2):183-186.

11. Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of bronchitis and emphysema*. Oxford, England: Oxford University Press, 1976.

12. Fligiel SEG, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana and/or tobacco. *Chest* 1997;112(2):319-326.

13. Hoffmann D, Brunnemann KD, Gori GB, Wynder EL. On the carcinogenicity of marijuana smoke. In Runecles VC, ed. *Recent advances in phytochemistry*. New York: Plenum Press, 1975, pp. 63-81.

14. Huber GL, Mahajan VK. The comparative response of the lung to marihuana or tobacco smoke inhalation. In Chesher G, Consroe P, Musty R, eds. *Marijuana: An international research report. Proceedings of Melbourne Symposium on Cannabis 2-4 September* (National Campaign Against Drug Abuse Monograph Series No. 7, pp. 19-24). Canberra: Australian Government Publishing Service, 1987.

15. Lee ML, Novotny M, Bartle KD. Gas chromatography/mass spectrometric and nuclear magnetic resonance spectrometric studies of carcinogenic polynuclear aromatic hydrocarbons in tobacco and marijuana smoke condensates. *Analytical Chemistry* 1976;48(2):405-416.

16. Leuchtenberger C, Leuchtenberger R. Cytological and cytochemical studies of the effects of fresh marihuana cigarette smoke on growth and DNA metabolism of animal and human lung cultures. In Braude MC, Szara S, eds. *The pharmacology of marijuana*. New York: Raven Press, 1976, pp. 595-612.

17. Llamas R, Hart DR, Schneider NS. Allergic bronchopulmonary aspergillosis associated with smoking moldy marijuana. *Chest* 1978;73(6):871-872.

18. Mattox KL. Pneumomediastinum in heroin and marijuana users. *Journal of the American College of Emergency Physicians* 1976;5(1):26-28.

19. Miller WE, Spiekerman RE, Hepper NG. Pneumomediastinum resulting from performing Valsalva maneuvers during marijuana smoking. *Chest* 1972; 62(2):233-234.

20. Newell GR, Mansell PW, Wilson MB, Lynch HK, Spitz MR, Hersh EM. Risk factor analysis among men referred for possible acquired immune deficiency syndrome. *Preventive Medicine* 1985;14(1):81-91.

21. Novotny M, Merli F, Weisler D, Fencl M, Saeed T. Fractionation and capillary gas chromatographic-mass spectrometric characterization of the neutral components in marijuana and tobacco smoke condensatres. *Journal of Chromatography* 1982;238:141-150.

22. Roth MD, Marques-Magallanes JA, Yuan M, Sun W, Sarafian TD, Hankinson O, Tashkin DP. Delta-9-tetrahydrocannabinol acts as both an inducer of the CYP1A1 gene and an inhibitor of cytochrome P4501A1 enzyme activity. In *1998 Symposium on the Cannabinoids*. Burlington, VT: International Cannabinoid Research Society, 1998, p. 69.

23. Roth MD, Yuan M, Mendenhall M, Kiertsher S, Tashkin DP. *Δ^9-THC suppresses antigen-induced proliferation and interferon-γ production by human T-cells*. Presented at the 1999 FASEB Summer Research Conference on "Pulmonary Pathophysiologic and Immune Consequences of Smoked Substance Abuse," Copper Mountain, CO, July, 1999.

24. Sherrill DL, Krzyzanowski M, Bloom JW, Lebowitz MD. Respiratory effects of nontobacco cigarettes: A longitudinal study in general population. *International Journal of Epidemiology* 1991;20(1):132-137.

25. Sherman MP, Campbell LA, Gong H Jr, Roth MD, Tashkin DP. Antimicrobial and respiratory burst characteristics of pulmonary alveolar macrophages recovered from smokers of marijuana alone, smokers of tobacco alone, smokers of marijuana and tobacco and nonsmokers. *American Review of Respiratory Disease* 1991;144(6):1351-1356.

26. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Jr. Marijuana use and cancer incidence. *American Journal of Public Health* 1997;8(5): 585-590.

27. Sridhar KS, Raub WA, Weatherby NL, Metsch LR, Surratt HL, Inciardi JA, Duncan RC, Anwyl RS, McCoy CB. Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age. *Journal of Psychoactive Drugs* 1994; 26(3):285-88.

28. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, Spivey GH, Gong H. Respiratory symptoms and lung function in habitual, heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *American Review of Respiratory Disease* 1987;135(1):209-216.

29. Tashkin DP, Simmons MS, Sherrill D, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV_1 with age: A longitudinal study. *American Journal of Respiratory and Critical Care Medicine* 1997;155(1):141-148.

30. Taylor FM. Marijuana as a potential respiratory tract carcinogen: A retrospective analysis of a community hospital population. *Southern Medical Journal* 1988;81(10):1213-1216.

31. Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR. The respiratory effects of cannabis dependence in young adults. *Addiction* 2000;95(11):1669-1677.

32. Tindall B, Philpot CR, Cooper DA, Gold J, Donovan B, Penny R, Barnes, T. The Sydney AIDS project: Development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. *Australian and New Zealand Journal of Medicine* 1988;18:8-15.

33. Wehner FC, Van Rensburg SJ, Thiel PC. Mutagenicity of marijuana and Transkei tobacco smoke condensates in the Salmonella/microsome assay. *Mutation Research* 1980;77(2):135-142.

34. Wu T-C, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine* 1988; 318:347-351.

35. Zhang Z-F, Morgenstern H, Spitz MR, Tashkin DP, Yu G-P, Marshall JR, Hsu TC, Schantz SP. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiology, Biomarkers and Prevention* 1999;8(12):1071-1078.

36. Zhu LX, Sharma S, Stolina M, Gardner B, Roth MD, Tashkin DP, Dubinett SM. Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB_2 receptor-mediated, cytokine-dependent pathway. *Journal of Immunology* 2000;165(1):373-380.

Chapter 30

Contaminants and Adulterants in Herbal Cannabis

John M. McPartland

INTRODUCTION

Medical marijuana, like any herbal product, may be tainted by potentially hazardous substances. These hazards can be classified into two groups. The first group, *natural contaminants,* primarily consist of thermal degradation products and microbial corruptions. Rarely, natural contamination with heavy metals poses a problem in plants grown in metal-rich soils. Siegel et al.,[33] for instance, documented natural bioaccumulation of mercury in Hawaiian marijuana. The second group consists of *artificial adulterants,* primarily pesticide residues and psychotropic substances. Consumers of medical marijuana, especially immunocompromised individuals, need to minimize their exposure to contaminants and adulterants. Harm-reduction strategies will be discussed.

NATURAL CONTAMINANTS

Toxins created by the combustion of cannabis can be considered contaminants. Pyrolysis creates at least 200 thermal degradation products in smoke not found in cannabis, including nasty mutagenic polycyclic hydrocarbons such as benz[α]anthracene, benzo[α]pyrene, napthalene, and several cresols and phenols[34] (see also Chapter 29). Marijuana smokers have implemented several strategies to decrease exposure to smoke contaminants. The most important strategy is to smoke high-THC cannabis. Less smoking is required. Marijuana *(ganja, sinsemilla)* contains 3 to 20 percent THC, whereas hashish *(charas)* contains up to 45 percent THC. Many patients filter cannabis smoke in water pipes. As Huber et al.[12] demonstrated, drawing

smoke through a water filter removes gas-phase smoke toxins, such as acetaldehyde, ammonia, benzene, carbon monoxide, hydrogen cyanide, and nitrosamines. But the aforementioned polycyclic hydrocarbons ("tars") are not readily removed by water pipes. Gieringer[10] found water pipes actually removed a greater percentage of THC than tars, making them counterproductive. To avoid exposure to tars, Gieringer recommended vaporizer devices, which heat marijuana to 180 to 190°C. This temperature vaporizes THC but is below the burning point of combustible plant material, so no "smoke" is produced. In Gieringer's lab, the best vaporizer delivered ten parts tar to one part cannabinoid, whereas cigarettes averaged 13:1, and pipes averaged 27:1 (the worst water pipe delivered a 40:1 ratio). Some patients avoid smoke toxins by eating marijuana in baked goods.

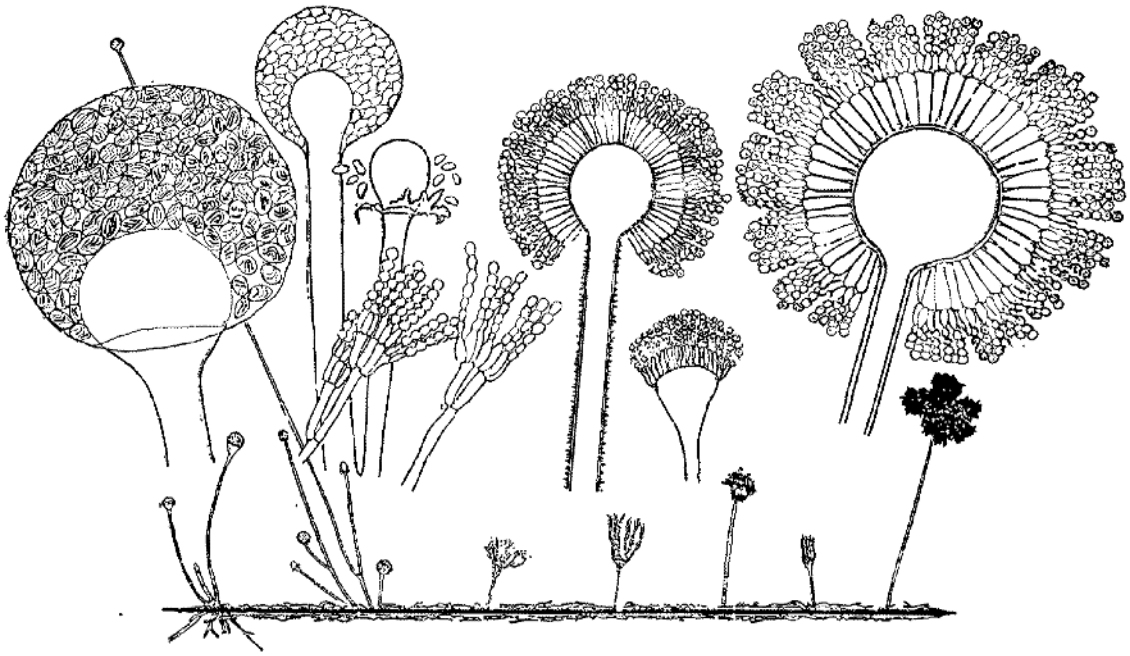
Ungerleider et al.[36] identified bacterial contaminants in marijuana cigarettes supplied by the National Institute of Drug Abuse (NIDA), including pathogenic *Klebsiella pneumoniae, Enterobacter cloacae,* group D *Streptococcus,* and some *Bacillus* species. From illicit marijuana, Taylor et al.[35] isolated *Salmonella muenchen,* and Kurup et al.[16] isolated *Thermoactinomyces candidus, Thermoactinomyces vulgaris,* and *Micropolyspora faeni.*

Spores of fungi infest cannabis (see Figure 30.1).[25] Accounts in the popular press describe molds that enhance the psychotropic effects of marijuana.[7,22] Marijuana users began exposing their marijuana to molds, hoping to increase the potency of their pot. As a result, Chusid et al.[3] extracted *Aspergillus fumigatus* from the lungs of a patient who buried his marijuana in the ground for "aging." Similarly, Llamas et al.[20] recovered *A. fumigatus* from marijuana owned by a patient suffering bronchopulmonary aspergillosis. Schwartz[32] scraped *Aspergillus flavus* from the sinuses of a marijuana smoker who suffered severe headaches. Other household molds that infest cannabis include *Aspergillus niger,*[14] *Aspergillus parasiticus,*[21] numerous *Mucor* species,[15,16] *Penicillium italicum,* and *Rhizopus stolonifer.*[26] Many field fungi also persist in harvested marijuana, such as *Histoplasma capsulatum,*[31] *Alternaria alternata,* and several *Fusarium* species.[24]

Kurup et al.[16] proved that fungal spores survive in smoke drawn from marijuana cigarettes. Most fungi are plant pathogens and their spores cannot infect healthy humans. But cases of immunosuppressed marijuana smokers contracting pulmonary fungal infections appear in the literature.[6,11,23,28]

Fungi incapable of infecting healthy hosts may still cause harm by producing toxins. *A. flavus,* for instance, produces aflatoxins in marijuana; the aflatoxins survive combustion in cigarettes.[21] Aflatoxins are acutely toxic (LD50 = 0.25 to 0.55 mg/kg, nearly 2,000 times more toxic than parathion, our most toxic insecticide), and carcinogenic. Some *Fusarium* species produce zearalenone, a toxin causing nausea, vomiting, and diarrhea. Other *Fusarium* toxins, the trichothecenes, cause a hemorrhagic syndrome and gained media attention for their reputed use in chemical warfare ("yellow

FIGURE 30.1. Opportunistic Fungi Isolated from Marijuana



Source: Line drawing by J. M. McPartland, from the *Mycology Society Newsletter* 1989;40:1. Reprinted with permission.

Note: Left to right: *Rhizopus stolonifer, Mucor hiemalis, Penicillium chrysogenum, P. italicum, Aspergillus flavus, A. fumigatus,* and *A. niger.* Top row: sporophores cross-sectioned to reveal internal structures (400x). Bottom row: natural habit of above fungi (25x).

rain"). *Alternaria alternata* frequently blights marijuana and produces a toxin called alternariol. Alternariol causes mutations in human esophageal epithelium, and may play an important role in cancer of the aerodigestive tract.[19] Aerodigestive tract tumors are the most common malignancies afflicting marijuana smokers (see McPartland and Pruitt[28] for a summary of 107 cancer cases appearing in the literature).

Prevention is the best strategy to avoid microbial contamination. One should harvest only disease-free cannabis, and harvested material should be air- or flue-dried. Sweat-cured cannabis (commonly imported from Colombia) maintains a "tradition" of *Aspergillus* contamination.[26] Properly dried cannabis contains 10 to 15 percent moisture content, and should be stored in a cold, dark place. Grossly contaminated marijuana is easy to diagnose, and should be discarded. Generally, black-market marijuana carries more microbiological contaminants than cannabis provided by the NIDA.[26]

Smoking contaminated cannabis with a water pipe does *not* protect smokers. Moody et al.[29] tested water pipes with *Aspergillus*-contaminated marijuana. Water pipes only reduced transmission of fungal spores by 15 percent. Suspect cannabis should be sterilized before smoking it. Baking marijuana in home ovens at 150°C (300°F) for five minutes kills spores of *A. fumigatus, A. flavus,* and *A. niger;* THC is not degraded nor vaporized by this method.[18] Ungerleider et al.[36] gas-sterilized marijuana in a mix of 12 percent ethylene oxide and 88 percent dichlorodifluromethane, at 8.5 to 10 psi, for 4.5 to 5 hours. They report no loss of THC from fumigation. They also sterilized marijuana with cobalt 60 irradiation (20,000 Gray Units), again without THC reduction.

ADULTERANTS

Farmers may spray plants during cultivation, and chemical residues may persist on harvested materials. Plants sprayed with foliar fertilizers may contain N-nitrosamines.[8] Pesticides sprayed on NIDA marijuana grown by the University of Mississippi included sulfur dusts, copper sulfate, and Ceresan M, a mercuric compound.[37] Historically, Indian entomologists sprayed cannabis with lead arsenate; the residue in 100 grams of ganja equaled 2.0 mg of arsenic, "allowed as a medical dose."[2] Cultivators of black-market marijuana apply a wide variety of insecticides and fungicides, including Acephate, aldicarb, carbaryl, Diazinon, malathion, maneb, parathion, and zineb.[9] Police spray plants with paraquat, glyphosate, or other herbicides. The contaminated crop may then be harvested and sold by unscrupulous drug dealers. This problem peaked around 1978, when 21 percent of marijuana tested in the southwestern United States was contaminated with paraquat.[17]

Drug dealers may deliberately adulterate cannabis with psychotropic substances. For the most part, this risky business belongs to history. Bell[1] analyzed a sample of hashish that contained about 25 percent opium, plus camphor. Historically, cannabis has been laced with tobacco, betel nut, foxglove leaves, henbane leaves, *Datura* leaves, and powdered *Nux vomica* seeds.[5] Thirty years ago, Johnson et al.[13] analyzed almost 8,000 samples of marijuana. In decreasing frequency of occurrence, adulterants included tobacco, phencyclidine (PCP), catnip, heroin, methamphetamine, parsley, LSD, oregano, tea, opium, alfalfa, peyote, mescaline, belladonna, water hemlock, cinquefoil, wild carrot, yellow chamomile, thyme, stramonium, and mugwort. Black marketeers of today may adulterate marijuana with diluents, such as hops, nettles, or oregano, to add weight.[30] Hashish diluents include candle wax, vegetable shortening, butter, ghee, henna powder, and finely powdered sand.[4]

Avoiding black-market adulterants is simple: secure a trustworthy supply of cannabis, or grow your own, organically.[27] Cannabis from government-supervised sources may be more reliable than black-market marijuana of unknown origin.

REFERENCES

1. Bell J. On the haschisch or *Cannabis indica*. *Boston Medical and Surgical* 1857;56:209-216.

2. Cherian MC. Pests of ganja. *Madras Agricultural Journal* 1932;20:259-265.

3. Chusid MJ, Gelfand JA, Nutter C, Fauci AS. Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease. *Annals of Internal Medicine* 1975;82(5):682-3.

4. Clarke RC. *Hashish!* Los Angeles, CA: Red Eye Press, 1998.

5. Cooke MC. *The seven sisters of sleep—History of the seven prevailing narcotics of the world*. London: James Blackwood, 1860.

6. Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *New England Journal of Medicine* 1991;324(10):654-662.

7. DuToit BM. *Cannabis in Africa*. Rotterdam: A.A. Balkema Press, 1980.

8. Farnsworth NR, Cordell GA. New potential hazard regarding use of marijuana—Treatment of plants with liquid fertilizers. *Journal of Psychedelic Drugs* 1976;8:151-155.

9. Frank M, Rosenthal E. *Marijuana grower's guide*. Berkeley, CA: And/Or Press, 1978.

10. Gieringer D. Marijuana research: Water pipe study. *Bulletin of the Multidisciplinary Association for Psychedelic Studies* 1996;6(3):59-66.

11. Hamadeh R, Ardehali A, Locksley RM, York MK. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. *Chest* 1988;94(3):432-433.

12. Huber GJ, First MW, Grubner O. Marijuana and tobacco smoke gas-phase cytotoxins. *Pharmacology, Biochemistry and Behavior* 1991;40(3):629-636.

13. Johnson DA, Gunn AB, Gunn JW. Dangerous drugs: Adulterants, diluents, and deception in street samples. *Journal of Forensic Sciences* 1972;17:629-639.

14. Kagen S. *Aspergillus:* An inhalable contaminant of marijuana. *New England Journal of Medicine* 1981;304(8):483-484.

15. Kagen SL, Kurup VP, Sohnle PG, Fink JN. Marijuana smoking and fungal sensitization. *Journal of Allergy and Clinical Immunology* 1983;71(4):389-393.

16. Kurup VP, Resnick A, Kagen SL, Cohen SH, Fink JN. Allergenic fungi and actinomycetes in smoking materials and their health implications. *Mycopathologia* 1983;82(1):61-64.

17. Landrigan PJ, Rowell KE, James LM, Taylor PR. Paraquat and marijuana: Epidemiologic risk assessment. *American Journal of Public Health* 1983;73(7): 784-788.

18. Levitz SM, Diamond RD. Aspergillosis and marijuana. *Annals of Internal Medicine* 1991;115(7):578-9.

19. Liu GY, Qian P, Zhang W, Dong YQ, Guo H. Etiological role of *Alternaria alternata* in human esophageal cancer. *Chinese Medical Journal* 1992;105:394-400.

20. Llamas R, Hart R, Schneider NS. Allergic bronchopulmonary aspergillosis associtated with smoking moldy marihuana. *Chest* 1978; 73(6):871-872.

21. Llewellyn GC, O'Rear CO. Examination of fungal growth and aflatoxin production on marijuana. *Mycopathologia* 1977; 62(2):109-112.

22. Margolis JS, Clorfene R. *A child's garden of grass*. New York: Ballantine Books, 1975.

23. Marks WH, Florence L, Lieberman J, Chapman P, Howard D, Roberts P, Perkinson D. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. *Transplantation* 1996; 61(12):1771-1774.

24. McPartland JM. Fungal pathogens of *Cannabis sativa* in Illinois. *Phytopathology* 1983; 72:797.

25. McPartland JM. Common names for diseases of *Cannabis sativa* L. *Plant Disease* 1991; 75:226-7.

26. McPartland JM. Microbiological contaminants of marijuana. *Journal of the International Hemp Association* 1994;1(2):41-44.

27. McPartland JM, Clarke RC, Watson DP. *Hemp diseases and pests*. Wallingford, UK: CABI Publications, 2000.

28. McPartland JM, PP Pruitt. Medical marijuana and its use by the immunocompromised. *Alternative Therapies in Health and Medicine* 1997; 3(3):39-45.

29. Moody MM, Wharton RC, Schnaper N, Schimpff SC. Do water pipes prevent transmission of fungi from contaminated marijuana? *New England Journal of Medicine* 1982; 306(24):1492-1493.

30. Phillips GF. Analytical and legislative aspects. In Brown DT, ed. *Cannabis*. Amsterdam: Harwood Academic Publishers, 1998, pp. 71-113.

31. Ramírez JR. Acute pulmonary histoplasmosis: Newly recognized hazard of marijuana plant hunters. *American Journal of Medicine* 1990; 88(Suppl. 5):60N-62N.

32. Schwartz IS. Marijuana and fungal infection. *American Journal of Clinical Pathology* 1985; 84(2):256.

33. Siegel BZ, Garnier L, Siegel SM. Mercury in marijuana. *Bioscience* 1988; 38:619-23.

34. Sparacino CM, Hyldburg PA, Hughes TJ. Chemical and biological analysis of marijuana smoke condensate. *NIDA Research Monograph* 1990; 99:121-140.

35. Taylor DN, Wachsmuth IK, Shangkuan Y-H, et al. Salmonellosis associated with marijuana. *New England Journal of Medicine* 1982; 306(27):1249-1253.

36. Ungerleider JT, Andrysiak T, Tashkin DP, Gale RP. Contamination of marihuana cigarettes with pathogenic bacteria – possible source of infection in cancer patients. *Cancer Treatment Reports* 1982; 66(3):589-591.

37. Yu S-L. "Fungi collected from *Cannabis sativa* grown in USDA gardens at the University of Mississippi." (Unpublished manuscript, University of Mississippi, 1973), 10.

Chapter 31

Practical Hints

Franjo Grotenhermen

DOSING

The threshold for typical psychic effects of cannabis lies in the range of about 0.2 to 0.3 mg Δ^9-THC/kg body weight or 5 to 10 mg/m^2 body surface area, respectively, or about 10 to 15 mg THC in an adult. However, this threshold may occasionally be lower, 5 mg THC per single dose, particularly in older individuals. Pronounced psychic effects after oral application are expected above 0.4 mg/kg. With inhalation, the threshold for perceivable effects may be lower, 5 mg or less.

Interindividual responsiveness is often very variable for therapeutic effects as well. Therefore, the optimal individual dose has to be ascertained. If possible, slowly increasing doses should be applied to avoid undesirable side effects, above all effects on psyche and circulation. Starting doses are 2 × 2.5 mg or 2 × 5.0 mg THC per day. Depending on need, dosages may be increased up to 5 × 10 mg/day or more. In some indications for therapeutic cannabis the starting doses remain sufficient, while in others, higher doses are required.

If natural cannabis products of unknown THC content are used orally, the patient should begin with about 0.05 to 0.1 g of the drug (for cannabis with an average THC content of 5 percent this corresponds to 2.5 to 5 mg THC) and increase slowly up to the desired or tolerated dose, respectively. With inhalation, one puff should be taken at first, followed by a period of pausing for several minutes to observe the effect. In this manner, the drug effect can be easily titrated. The customary psychotropic effects of cannabis may be tolerable with acute treatment in some contexts, such as in the treatment of a migraine attack. Side effects may also be avoided with oral administration before bed, e.g., to prevent nocturnal spasms in MS patients.

Tolerance develops to the psychic and cardiac effects of cannabis within some days or weeks of chronic usage, so that daily doses of more than 50 mg THC may sometimes be taken without relevant psychic side effects. Tolerance may remain for a relatively long period (weeks to months) after quitting the drug. Tolerance may also arise with respect to therapeutically desired effects and prompt an increase in dose. Alternatively, a cessation of cannabis therapy for a period of two to three months with change to another medication may be considered.

RESTRICTIONS ON USE AND HELPFUL HINTS

THC and cannabis are absolutely contraindicated in hypersensitivity to THC (rare).

Relative contraindications are severe psychiatric diagnoses. Particularly, schizophrenic psychosis, mania, and endogenous depression may be exacerbated. However, a positive influence on several psychotic symptoms has been occasionally reported. No influences on physical fetal development in children born to chronic cannabis users have been reported. Yet, as far as possible, cannabis should be avoided during pregnancy and in lactating women because of the controversial evidence for subtle disturbances of cognitive development. Because of possible influence on the endocrine system in adolescents and psychic effects, chronic medication with cannabinoids in children and adolescents above the psychotropic threshold should also be avoided. However, due to the lower number of brain cannabinoid receptors in children, psychic effects appear only at higher doses compared to adults. Thus, in rats, cannabinoid receptor binding in different brain areas was found to increase fivefold between birth and postnatal day 60.[2] In a clinical study with children, high doses of THC were tolerated well.[1]

Patients with heart disease (severe arrhythmia, coronary artery disease) should avoid overdosing since the use of cannabis might increase the risk for heart attacks. Doses should be increased only slowly precluding any relevant effect on circulation. Tolerance develops to these effects within days or weeks.

Thorough information on possible psychic side effects should be provided by the physician so that the patient will not be surprised by any altered state of consciousness that is encountered subsequent to cannabis/THC medication. The ability to operate machinery and to drive a car is impaired in a dose-dependent manner. Patients should be warned of such dangerous activities until they tolerate the drug.

In addition, attention should be paid to possible additive effects of cannabis with other sedating medicaments such as opiates and benzodiazepines. Patients should be informed of the possible development of tolerance, dependency, and withdrawal symptoms in long-term therapy as well as possible psychic and physical rebound effects (see Chapters 21 and 23).

With oral use of cannabis products, absorption varies individually, and idiosyncratically. Patients should be informed of the delayed onset of action 30 to 60 (to 120) min. Inhalation has pharmacokinetic advantages, but introduces risks to mucous membranes of the respiratory tract and the upper gastrointestinal tract (see Chapter 29).

TREATMENT OF AN ACUTE OVERDOSE

In acute dysphoric states following THC/cannabis ingestion, the patient should be brought to a quiet place and "talked down." Usually, this is sufficient while the drug activity dissipates. Most undesirable symptoms will disappear as well. If necessary, benzodiazepines (diazepam up to 10 mg iv) may be administered. Tachycardia may be treated with a beta-blocker (propranolol iv).[14]

INTERACTIONS

Dronabinol has been used in combination with a multitude of medications without significant deleterious drug interactions. Clinical studies in the beginning of the twentieth century often demonstrated mutual enhancement of therapeutic effects of natural cannabis preparations and other drugs (see Chapter 4). In modern therapeutic concepts a combination of cannabis/THC with other medications could also be of benefit for many indications. Cannabis has been used illegally by individuals suffering from many diseases concomitantly with numerous prescription medicines. No unwanted side effects of clinical relevance have been observed to date.[9]

Some interactions and mechanisms are known (see Chapters 5 and 7). Interactions with other drugs may be based on similar activity or metabolic concurrence.[16] Since THC strongly binds to proteins, interactions with other protein-binding drugs may be possible. However, there is no evidence from in vivo studies for this assumption. Other medicines may enhance or attenuate certain actions of cannabis/THC or certain actions of these medicines may be enhanced or attenuated by cannabis/THC. Moreover, it is possible that certain effects are enhanced and others reduced, as is the case with phenothiazines applied against side effects of cancer chemotherapy (see Chapter 14).

Of greatest clinical relevance is reinforcement of the sedating effect of other psychotropic substances (alcohol, benzodiazepines), and the interaction with substances that act on the heart (amphetamines, adrenaline, atropine, beta-blockers, diuretics, tricyclic antidepressants, etc.). The metabolism of theophylline may be accelerated, while the clearance of antipyrine and barbiturates may be delayed.

A number of additive effects may be desirable, such as the enhancement of the analgesic effect of the opiates and the antiemetic effect of the phenothiazines for muscle relaxation, anticonvulsant properties, bronchodilation, and in decreasing elevated intraocular pressure.*

- *Anticholinergics:* Atropine and scopolamine may increase the tachycardic action of THC.
- *Anticholinesterases:* Physostigmine antagonizes psychotropic and tachycardic effects of THC.[17] Physostigmine given before THC enhanced the cataleptic effects of THC in mice. This effect was attenuated by atropine.[15]
- *Antidepressants (selective serotonin reuptake inhibitors):* THC may increase the effect of fluoxetine.
- *Antidepressants (tricyclics):* Tachycardic, hypotensive, and sedating effects of amitriptyline may be enhanced.
- *Barbiturates:* CNS depression may be enhanced. Barbiturates may reinforce the tachycardic effects of THC. The clearance of barbiturates may be acutely decreased and enhanced with chronic use.
- *Benzodiazepines:* CNS and respiratory depression may be increased. The antiepileptic action may be enhanced.[10]
- *Beta-blockers:* Reduce THC-associated tachycardia.
- *Cocaine:* Nasal absorption of cocaine and tachycardia may be enhanced.
- *Dopamine agonists:* Experimental studies suggest that dopamine D_2 receptor agonists might increase the analgesic effects of THC.[4]
- *Ethanol:* CNS impairment may be enhanced.
- *Glaucoma:* Several drugs that decrease intraocular pressure and cannabinoids may act additively.[7]
- *Ketamine:* Possible additive CNS depression.
- *Neuroleptics:* THC may antagonize the antipsychotic actions of neuroleptics. It may improve their clinical responsiveness in motor disorders.[11]
- *Nonsteroidal anti-inflammatory drugs (NSAIDs):* Indomethacin, acetylsalicylic acid, and other NSAIDs antagonize THC effects. Indomethacin significantly reduced subjective "high" and tachycardia.[13]
- *Opiates:* Enhancement of sedation and analgesia[18] (see also Chapters 8 and 15).
- *Phenothiazines:* Prochlorperazine and other phenothiazines attenuate the psychotropic effects of THC and increase its antiemetic effects (see Chapter 14).

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*If no source is given, references for the following interactions are found in the articles by Sutin and Nahas[17,9] or by Hollister[8].

- *Reserpine:* THC increased reserpine-induced hypokinesia in rats.[12]
- *Sympathomimetics:* Additive tachycardia and hypertension with amphetamines and epinephrin.
- *Theophylline:* Due to accelerated metabolism of the medicament higher doses might be necessary.

CANNABIS OR THC

The main pharmacological activity of cannabis depends primarily on its THC concentration. There is no evidence that acetone-treated cigarettes made from cannabis devoid of THC exert significant pharmacological effects.[6] Thus, such preparations have been employed as placebo cigarettes in comparison to marijuana in clinical trials. The primary pharmacological effects of THC may be modulated by other active compounds. Most pharmacologically active constituents of the cannabis plant probably produce only strong effects in doses above those that can be easily ingested with natural cannabis products (see Chapters 33 and 37). Without its specific cannabinoid contributions, cannabis presumably would provoke pharmacological effects more akin to other common plants, such as peppermint or hops *(Humulus),* the latter being the botanically closest relative to hemp.

THC and cannabis may be considered equivalent with regard to clinical indications. Some authors object to the fact that herbal cannabis has unknown composition, the same argument advanced in opposition to the medical use of herbs, in general. The modern paradigm of drug treatment, particularly in the United States, that demands a selective pharmacological effect through the use of defined single chemical agents is in fact pervasive, but without a strong basis. Many herbal products in Europe are standardized and have been clinically proven in double-blind placebo-controlled trials. In actuality, the individual reaction of a patient to 10 mg dronabinol is just as uncertain, variable, and idiosyncratic as the pharmacological effects obtained with a herbal cannabis preparation standardized to 10 mg THC content. Drug therapy is not mathematics, but has always pertained to interindividual and intraindividual variability of numerous parameters: age, gender, general health status, concomitant disease, interaction with other drugs, absorption, function of digestion, liver, kidneys, etc. The variability of the components of cannabis with the exception of THC and perhaps CBD probably does not play a major role in the reproducibility of an already observed effect in comparison to other parameters.

Indeed, acceptance or rejection of natural cannabis products is not rooted in the composition of the drug, but in disadvantages or advantages of the inhalation route of administration. Occasionally, differences between THC and cannabis with claimed advantages for whole plant preparations are reported. These are all anecdotal in nature. Controlled studies to compare

THC (dronabinol) and whole plant preparations are currently lacking, but the first such studies have been started in Central Europe at the time of this book's preparation.

SMOKING OR EATING

Both cannabis and THC can be administered by oral, inhalation, sublingual, and rectal routes. In experimental studies, other applications have also been used (iv, intrathecal, intraperitoneal, etc.). In current recreational and therapeutic usage, inhalation and oral use play the major roles, having particular advantages and disadvantages.

Natural cannabinoids must be decarboxylated before ingestion. The simplest and fastest way to achieve this is through heating (smoking, baking, cooking). In the plant, most of Δ^9-THC is present as the pharmacologically inactive acid form, as one of two Δ^9-THC carboxylic acids (THCA). Neutral phenols are responsible for the known biological effects of cannabis. Five minutes of heating to 200 to 210°C have been determined as optimal condition for decarboxylation.[3] In smoking cannabis, where temperatures of 600°C are achieved, only a few seconds of combustion are apparently sufficient for decarboxylation.

Depending on method of administration, there are significant differences in absorption and metabolism of THC and attendant effects, time until onset of action, and its duration (see Chapter 6 and Table 31.1). After smoking, subjective effects are perceived within seconds to minutes, achieve their maximum after 30 min and last 2 to 3 h. After eating, onset of effects are delayed for 30 min to 2 h, are more constant, last longer, and fade more slowly, over 5 to 8 h, or even longer with very high doses. The graphed curve of THC concentration in the blood is also flatter.

If cannabis is taken orally, lipophilic THC is absorbed better by the intestinal mucosa if some fat is ingested simultaneously. Therefore, some cream can be added if cannabis is taken as a tea, or a recipe with plenty of butter can be used if the drug is baked in cookies. The advantage of oral intake is its more constant and longer activity, for example in the prevention of nocturnal complaints and pain. Its disadvantage is the impaired regulations of dosing, especially with cannabis of unknown THC content.

Due to the faster onset of action, inhalation of cannabis allows good titration of the required dose. This is an advantage in acute disorders that demand a fast effect, e.g., in the beginning of a migraine attack. The disadvantage of smoking is irritation and potential damage to the respiratory tract (see Chapter 29). Therefore, cannabis strains with high THC content are preferred in therapeutic use to cover the entire daily medical dosage of THC with a fraction of a gram of herbal cannabis. The duration of breath holding does not have a major influence on the absorbed amount of THC as is often assumed by cannabis

TABLE 31.1. Comparison of the Effectiveness of THC Application to Humans via Relevant Routes

Parameter	Intravenous	Inhaled	Oral (lipophilic vehicle)
Systemic bioavailability	100%	10-30 (-50)%	10-20%
Psychotropic threshold per kg body weight	0.01/.02 mg/kg	0.03-0.1 mg/kg	0.2-0.3 mg/kg
Psychotropic threshold per individual	1 mg	2-4 mg	ca. 10-20 mg
Maximum plasma concentration at the psychotropic threshold	ca. 20-50 ng/ml	ca. 20-50 ng/ml	ca. 5 ng/ml
Dose for a marked intoxication	2-4 mg	10-20 (-50) mg	30-40 (-90) mg

users, yet long and deep inhalation with the Valsalva maneuver increases the risk of producing a pneumothorax (see Chapter 29). Inhalation devices or vaporizers reduce the intake of damaging combustion products, but possibly not to a sufficient extent (see Chapter 30).

STORAGE

Slow decarboxylation of Δ^9-THC occurs at room temperature. Thus, in a study by Brenneisen et al., after one year of storage, 50 percent of THCA in marijuana was converted into neutral THC.[3] However, storage leads to a decrease in cumulative THC content through oxidation of THC to the pharmacologically far less active CBN.[5]

Within 47 weeks, the THC content of marijuana decreased by 7 percent with dark, dry storage at 5°C, and by 13 percent at a temperature of 20°C.[5] With additional light exposure, the loss increased threefold to 36 percent.

Therefore, cannabis products should be stored in a dry, dark, cool place with exclusion of air. This way they can be stored for several years without great loss of activity.

CULTIVATION

Cannabis plants have been selectively bred that produce a THC content in dry material of 5 to 10 percent, even outdoors in temperate regions. The purchase and sale of hemp seeds for drug production are prohibited in most

countries, as is plant cultivation. Some simple principles of cannabis cultivation are presented in the following paragraphs (see Chapter 1 for vegetative plant production). More information can be found in the literature.

For germination, cannabis seeds are soaked in water for about 24 h and then put into moist compost, leaf-mold, or potting soil in a small flowerpot. Make sure that the seeds neither dry out nor swim in water.

The plant seedlings require 15 to 18 h of natural or artificial light. A sunny balcony or placement under fluorescent tube fixtures, which hang directly above the plants, are suitable. As soon as the plants have reached a few centimeters in height, they can be replanted into a flowerpot about 20 liters in size. After transplanting, the plant should be watered. Subsequently, the plant should be watered whenever the upper layer of soil is dry. Ideally, the flowerpot should absorb surplus water from the underlying mat or tray within a few minutes. Very basically, the soil should be moist but not wet.

When the plant possesses six to seven pairs of leaves (after about four weeks), the two top pairs are pruned off closely above the next pair down. This results in bushy growth with more female flowers. If the plants grow quickly, it is possible to prune a second time. Bloom starts after two to four months depending on genetic varieties and external growth conditions, but in most instances is triggered by shorter days with 12 h or less of light exposure.

REFERENCES

1. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sciences* 1995;56(23-24):2097-2102.

2. Belue RC, Howlett AC, Westlake TM, Hutchings DE. The ontogeny of cannabinoid receptors in the brain of postnatal and aging rats. *Neurotoxicology and Teratology* 1995;17(1):25-30.

3. Brenneisen R. Psychotrope Drogen. II. Bestimmung der Cannabinoide in *Cannabis sativa* L. und in Cannabisprodukten mittels Hochdruckflüssigkeitschromatographie (HPLC). [Determination of cannabinoids in *Cannabis sativa* L. and in cannabis products by high-performance liquid chromatography (HPLC)]. *Pharmaceutica Acta Helvetiae* 1984;59(9-10):247-259.

4. Carta G, Gessa GL, Nava F. Dopamine D_2 receptor antagonists prevent delta-9-tetrahydrocannabinol-induced antinociception in rats. *European Journal of Pharmacology* 1999;384(2-3):153-156.

5. Fairbairn JW, Liebmann JA, Rowan MG. The stability of cannabis and its preparations on storage. *Journal of Pharmacy and Pharmacology* 1976;28(1):1-7.

6. Grotenhermen F, Karus M. Industrial hemp is not marijuana. Comment on the drug potential of fibre Cannabis. *Journal of the International Hemp Association* 1999;5(2):96-101.

7. Hepler RS, Petrus RS. Experiences with administration of marihuana to glaucoma patients. In Cohen S, Stillman R, eds. *Therapeutic potential of marihuana*. New York: Plenum, 1976.

8. Hollister LE. Interactions of cannabis with other drugs in man. *NIDA Research Monograph* 1986;68:110-116.

9. Hollister LE. Interactions of marihuana and Δ^9-THC with other drugs. In Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999, pp. 273-277.

10. Koe BK, Milne GM, Weissman A, Johnson MR, Melvin LS. Enhancement of brain [3H]flunitrazepam binding and analgesic activity of synthetic cannabimimetics. *European Journal of Pharmacology* 1985;109(2):201-212.

11. Moss DE, Manderscheid PZ, Montgomery SP, Norman AB, Sanberg PR. Nicotine and cannabinoids as adjuncts to neuroleptics in the treatment of Tourette's syndrome and other motor disorders. *Life Sciences* 1989;44(21):1521-1525.

12. Moss DE, McMaster SB, Rogers J. Tetrahydrocannabinol potentiates reserpine-induced hypokinesia. *Pharmacology, Biochemistry and Behavior* 1981;5(5):779-783.

13. Perez-Reyes M, Burstein SH, White WR, McDonald SA, Hicks RE. Antagonism of marihuana effects by indomethacin in humans. *Life Sciences* 1991;48(6): 507-515

14. Perez-Reyes M. The psychologic and physiologic effects of active cannabinoids. In Nahas G, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999, pp. 245-252.

15. Pertwee RG, Ross TM. Drugs which stimulate or facilitate central cholinergic transmission interact synergistically with delta-9-tetrahydrocannabinol to produce marked catalepsy in mice. *Neuropharmacology* 1991;30(1):67-71.

16. Pryor GT, Husain S, Mitoma C. Acute and subacute interactions between delta-9-tetrahydrocannabinol and other drugs in the rat. *Annals of the New York Academy of Sciences* 1976;281:171-189.

17. Sutin KM, Nahas GG. Physiological and pharmacological interactions of marihuana (Δ^9-THC) with drugs and anesthetics. In Nahas G, Sutin KM, Harvey DJ, Agurell S., eds. *Marihuana and medicine*. Totowa, NJ: Humana Press, 1999, pp. 253-271.

18. Welch SP, Eads M. Synergistic interactions of endogenous opioids and cannabinoid systems. *Brain Research* 1999;848(1-2):183-190.

PART V:
OTHER CANNABINOIDS

Chapter 32

Overview of Cannabinoids Under Investigation

Franjo Grotenhermen

In addition to dronabinol (Δ^9-THC) and natural cannabis preparations, a multitude of other substances are currently being investigated with regard to their therapeutic qualities. They are intended to optimize medicinal effectiveness and reduce side effects of cannabinoids and cannabis preparations currently used for therapeutic purposes[1,4,5] (see also Chapters 2 and 7).

The following are among the substances currently in experimental and clinical investigations:

- Nonpsychotropic phytocannabinoids (see Chapter 33)
- Nonpsychotropic metabolites of Δ^9-THC or related compounds, respectively (see Chapter 35)
- Endocannabinoids and analogues (see Chapter 34)
- Cannabinoids or cannabinoid-like compounds that do not act through CB receptors but through different mechanisms (see Chapter 36)
- Substances that influence transport and metabolism of endocannabinoids[3]
- Antagonists of the CB_1 or CB_2 receptor, respectively, which block the natural action of endocannabinoids[2]

One review considers a number of patented substances that act in distinct ways on the cannabinoid receptor system.[1] Among current patent holders are Eli Lilly and Company, Yissum Research Development Company, Pfizer, Inc., Merck Frosst Canada, Inc., David W. Pate, Lifegroup Spa, Sterling Drug Company, Sanofi-Synthelabo SA, Japan Tobacco Inc., University of Connecticut, and Pharmos Corporation. Among the claimed or presumed indications are the following:

- Neuroprotection (dexanabinol, see Chapter 36)
- Analgesia, inflammation (CT3, see Chapter 35)
- Inflammation, migraine, spasticity, glaucoma, multiple sclerosis (anandamide derivatives, see Chapter 34)
- Inflammation, immunosuppression, allergy, infection, analgesia (selective CB_2 receptor agonists)
- Viral and bacterial meningitis, rheumatoid arthritis, multiple sclerosis (palmitylethanolamide)
- Depression, CNS disorders (selective CB_2 receptor ligands)
- Psychosis, eating disorders, memory disorders, senile dementia, Alzheimer's disease (CB_1 antagonists)
- Autoimmune diseases (rheumatoid arthritis, MS, psoriasis, asthma), infections (CB_2 antagonists)
- Vascular disorders (CB_2 antagonists)

The compounds discussed in Chapters 33 to 36 are under clinical investigation or soon will be. Other substances are also being evaluated, such as the anandamide analogue ALIAmide (palmidrol) intended to treat chronic inflammation or autoimmune diseases, respectively.[1]

REFERENCES

1. Barth F. Cannabinoid receptor agonists and antagonists. *Expert Opinion on Therapeutic Patents* 1998;8:301-313.

2. Barth F, Rinaldi-Carmona M. The development of cannabinoid antagonists. *Current Medicinal Chemistry* 1999:6(8):745-755.

3. Di Marzo V, Bisogno T, De Petrocellis L, Melck D, Martin BR. Cannabimimetic fatty acid derivatives: The anandamide family and other endocannabinoids. *Current Medicinal Chemistry* 1999;6(8):721-744.

4. Pertwee RG. Cannabinoid receptor ligands: Clinical and neuropharmacological considerations relevant to future drug discovery and development. *Expert Opinion on Therapeutic Patents* 1996;5:1245-1253.

5. Seltzman HH. Structure and receptor activity for classical cannabinoids. *Current Medicinal Chemistry* 1999;6(8):685-704.

Chapter 33

Cannabidiol: Possible Therapeutic Application

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Viviane M. C. Guimarães
Elaine A. Del Bel

Delta-9-tetrahydrocannabinol (Δ^9-THC) is commonly accepted as the major psychoactive constituent of *Cannabis sativa*. However, other components of the plant such as cannabidiol (CBD, see Figure 33.1) can influence its pharmacological activity.[6,24,26]

CBD, which constitutes up to 40 percent of marijuana extracts[13] is devoid of the typical marijuana psychological effects,[45] but may interact with Δ^9-THC.[24,3,12,25,20,10,45] Although potentiation of Δ^9-THC effects has been found, this probably involves pharmacokinetic interactions since CBD is a potent inhibitor of hepatic drug metabolism[32,4] and increases Δ^9-THC concentrations in the brain.[23] Several studies, however, have reported antagonism of Δ^9-THC effects when both compounds are administered concomitantly.[24,11,41,46,43]

In a study conducted by Zuardi et al.[45] the simultaneous oral administration of CBD (1 mg/kg) with a high Δ^9-THC dose (0.5 mg/kg) in healthy volunteers attenuated the anxiogenic and psychotomimetic symptoms induced by Δ^9-THC, but not the increase in pulse rate. Considering that the dose of

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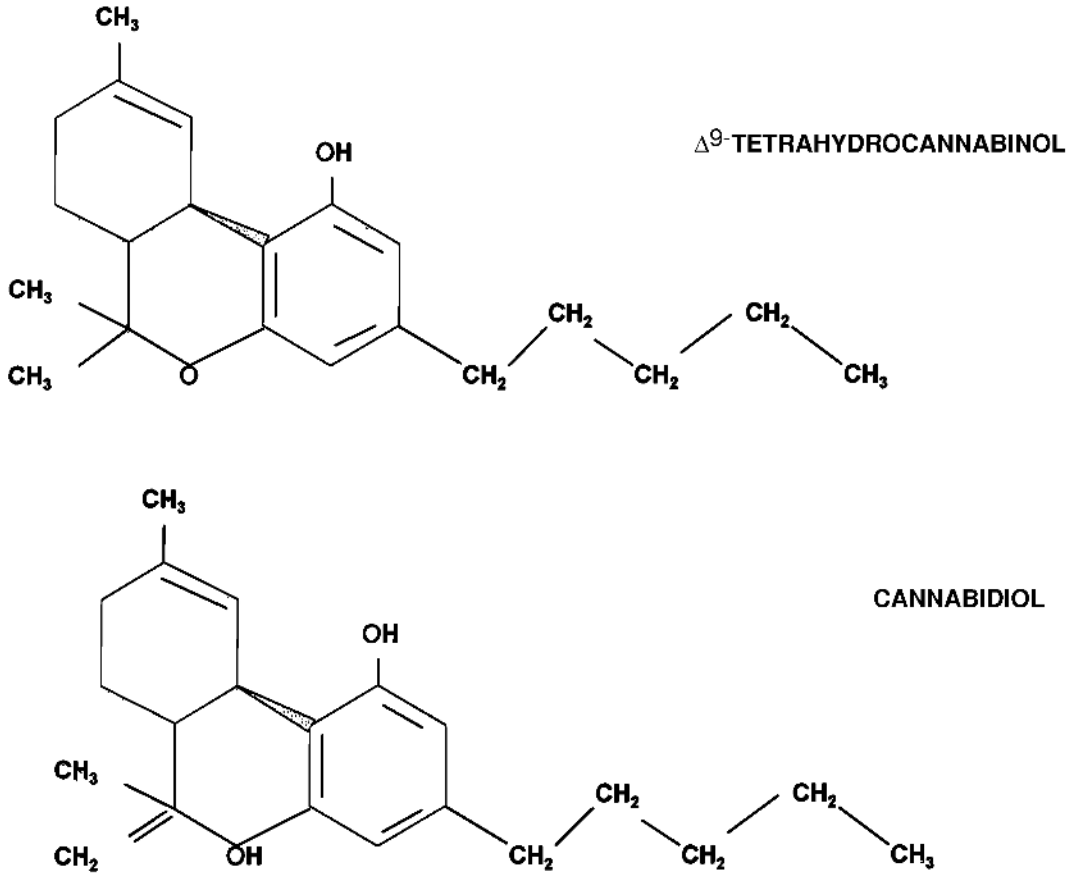
FIGURE 33.1. Chemical Structure of Cannabidiol and Δ^9-Tetrahydrocannabinol



CBD used in this study does not change Δ^9-THC blood levels,[1] it was suggested that CBD blocked Δ^9-THC effects through some intrinsic pharmacological properties. Actually, sedative,[34,41,45] hypnotic,[28,7] anticonvulsant,[5,22,9] neuroprotective,[17] and hormonal effects[46,42] of CBD alone have been reported in both laboratory animals and humans.

ANXIOLYTIC PROPERTIES OF CBD

An initial report showed anxiolytic effects of this compound (10 mg/kg) in a conditioned emotional response paradigm.[43] Similar anxiolytic results were reported by Musty et al.,[30] using the Vogel conflict test, and by Guimarães et al.[14] and Onaivi et al.,[31] employing the elevated plus maze test. In the study by Guimarães et al.[14] the effective doses of CBD ranged from 2.5 to 10 mg/kg. The drug effect had an inverted U shape, and higher doses were no longer effective. This could help to explain the negative results obtained with high doses of CBD (above 100 mg/kg) in a Geller-Seifter conflict test.[36] Anxiolytic effects over a limited range of doses were

also reported for three derivatives of CBD, HU-219, HU-252, and HU-291, in the elevated plus maze.[15]

Based on these preclinical studies, and considering that CBD-adverse effects have been extensively investigated in laboratory animals and humans,[9,25,10,8,27] the presence of anxiolytic properties of CBD were tested in healthy volunteers submitted to a simulated public speaking test (SPS).

In this model, subjects were asked to perform a speech in front of a video camera. The procedure increases subjective anxiety and its physiological concomitants, and is sensitive to anxiolytic and anxiogenic compounds.[16,40,18] CBD (300 mg, p.o.) was compared, under a double-blind design, to ipsapirone (a 5HT1A partial agonist, 5 mg), diazepam (anxiolytic benzodiazepine, 10 mg), or placebo. The results showed that both CBD and the two other anxiolytic compounds attenuated anxiety induced by the test.[40] At this dosage, CBD did not induce any significant sedative effects. The results, therefore, support the claim of anxiolytic properties of CBD.

ANTIPSYCHOTIC EFFECT OF CBD

In the initial study by Zuardi et al.[45] CBD was also able to attenuate the psychotomimetic effects of Δ^9-THC. To investigate a possible antipsychotic action, the effects of CBD and haloperidol, a typical antipsychotic drug, were compared in animal models. Both drugs attenuated stereotypy (that is, repetitive movements such as sniffing or biting, made without a clear objective) induced by a dopaminergic agonist, apomorphine. CBD, however, did not induce catalepsy at any dose tested (15 to 480 mg/kg) and had a very low potency to increase prolactin levels.[39]

The ability of typical antipsychotics to induce catalepsy in rodents is highly correlated with the appearance of parkinson-like symptoms in patients treated with these drugs. The profile of CBD effects in these tests, therefore, is similar to that seen with the atypical antipsychotic such as clozapine.

In continuation of this preclinical study, CBD effects were verified in a schizophrenic patient who had significant hormonal side effects during treatment with a typical antipsychotic.[44] The patient, a 19-year-old woman, was referred to the inpatient unit of the Clinical Hospital of Ribeirão Preto because of aggressiveness, self-injury, incoherent thoughts, and auditory hallucinations. After study protocol approval by the local ethical committee, informed consent was obtained from close relatives. The study began with a four-day wash-out hospitalization period in which the patient received placebo plus the usual support measures. From days 4 to 30 she received CBD in progressively increasing dosage, up to 1,500 mg/day (in two divided doses). CBD was then stopped and replaced by placebo for four days. After that, haloperidol administration was started. Dosage adjustment was based

on clinical evaluation. Diazepam was also administered in periods of great agitation. The mean daily dose of diazepam decreased after the beginning of CBD treatment from 16.3 to 5.7 mg/day. Two psychiatrists and two nurse auxiliaries evaluated the patient and the interviews were videotaped. At the end of the study, the videotapes were analyzed blindly and in a random sequence by another psychiatrist. Symptoms decreased after CBD treatment and there was a trend for worsening of the symptoms after drug withdrawal. The improvement obtained with CBD was not increased by haloperidol. This improvement was seen in all items of the rating scale employed, including those more closely related to psychotic symptoms, making it improbable that an anxiolytic action was the sole factor responsible for the antipsychotic effect. The drug was well tolerated during the study, and no parkinson-like symptoms were reported.[44]

FOS-*LIKE IMMUNOREACTIVITY EXPRESSION INDUCED BY CBD*

Different stimuli, including stress, seizure, drugs, pain, light, or odors are able to induce *c-fos* expression in different brain regions, reflecting specific neuronal functional activation.[29]

Typical (haloperidol) and atypical (clozapine) antipsychotics have been shown to induce distinct patterns of *c-fos* expression in the brain.[35] For example, haloperidol induces strong *Fos*-like immunoreactivity (FLI) in the dorsal striatum and nucleus accumbens, whereas clozapine induces FLI in the nucleus accumbens and prefrontal cortex but not in the dorsal striatum. No study has so far tested the effects of CBD on the expression of FLI. Therefore, we decided to verify this expression and compare it with that induced by haloperidol or clozapine.

In brief, male Wistar rats (200 to 250 g) with free access to water and food were kept in a 12 h light-dark cycle (lights on at 7:00 a.m.), under controlled temperature. The animals received i.p. injections of CBD (120 mg/kg, N = 5), clozapine (20 mg/kg, N = 4), haloperidol (1 mg/kg, N = 4), or vehicle (N = 5). The doses of clozapine and haloperidol were based on the study by Robertson and Fibiger.[35] Two hours after the treatment the rats were anesthetized with i.p. injections of urethane 25 percent (2.5 ml/kg), and transcardiacly perfused with saline followed by 4 percent paraformaldehyde. After removal, the brains were kept in 4 percent paraformaldehyde for 2 h and then remained overnight in 30 percent sucrose solution. Afterward, 40 μM coronal sections were obtained in a cryostat and processed for *Fos* immunohistochemistry, as described by Silveira et al.[37] Tissue sections were successively washed and incubated for 40 h with the primary *Fos* antibody (1:2000, Cambridge Research Biochemicals). Sections were then processed by the avidin-biotin immunoperoxidase method, and FLI was revealed by addition of the

chromogen 3,3'-diaminobenzidine (DAB, Sigma) and hydrogen peroxide. The slices were mounted on slides and cover-slipped for microscopic observation. FLI could be visualized as a brown reaction product inside neuronal nuclei, whose location was determined with Paxinos and Watson's atlas (1986). FLI in the dorsal striatum, the shell of the nucleus accumbens, prefrontal cortex, and lateral septal nucleus were counted in a fixed area by JAVA computerized image analysis program.

CBD and clozapine induced FLI in the prefrontal cortex and lateral septal nucleus, but not in the dorsal striatum. FLI in the latter region was induced by haloperidol. This drug also induced FLI in the lateral septal nucleus, but not in the prefrontal cortex (see Figures 33.2, 33.3, and 33.4). All compounds tended to induce FLI in the nucleus accumbens, but the differences did not reach the significance level.

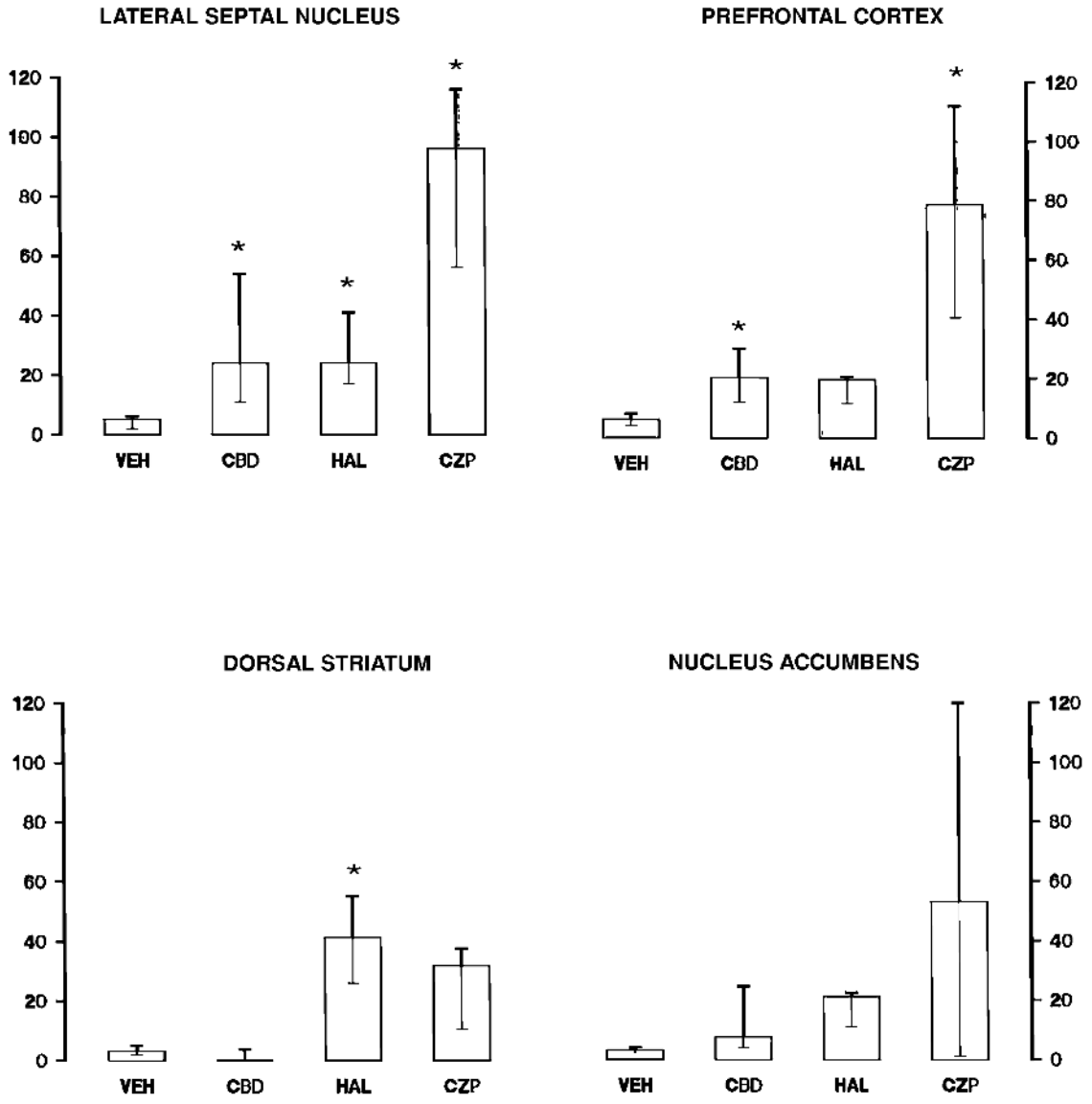
These results showed, for the first time, that CBD is able to induce FLI in the central nervous system. The effective CBD dose was similar to that showing antipsychotic effects in animal models.[44] In this latter study, CBD had pharmacological effects similar to clozapine. In our study, the FLI expression pattern was also similar between the two drugs and no significant expression was found in the dorsal striatum.

Recently, Alonso et al.[2] showed that SR141716, a cannabinoid receptor antagonist, is able to induce FLI in limbic areas such as the prefrontal cortex, the shell of the nucleus accumbens, the ventro lateral septum, and the dorsomedial caudate-putamem, but not in motor-related areas such as the core of the nucleus accumbens, and dorsolateral caudate-putamem. These results are remarkably similar to ours, and suggest that CBD might act as an antagonist of endogenous cannabinoids. These substances have been proposed to play a role in schizophrenia.[19] Although CBD is not a potent antagonist of these receptors,[21] recent studies have shown that CBD may behave as an antagonist of Δ^9-THC at micromolar range.[33,38]

CONCLUSIONS

Although the mechanisms of CBD action are still unclear, a considerable body of evidence reviewed in this chapter suggests that it has biological effects, particularly anxiolytic and/or antipsychotic properties. Clinical trials are clearly needed to confirm these possible effects.

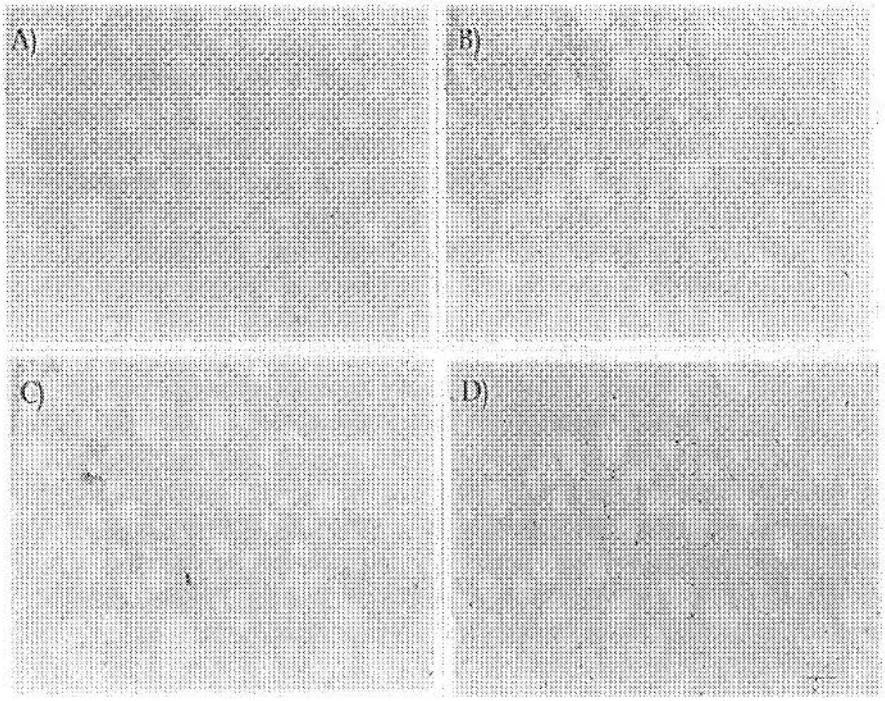
FIGURE 33.2. Number of *Fos*-Like Immunoreactive Neurons (in 0.1 mm^2) in the Septal Lateral Nucleus, Prefrontal Cortex, Dorsal Striatum, and Nucleus Accumbens of Rats (N = Four to Five/Group) Treated I.P. with Vehicle (VEH), Cannabidiol (CBD, 120 mg/kg), Haloperidol (HAL, 1 mg/kg) or Clozapine (CZP, 1 mg/kg)



Note: The animals were killed 2 h after treatment and their brains removed and processed for *Fos* immunohistochemistry. Results are expressed as the median ± interquartile interval.

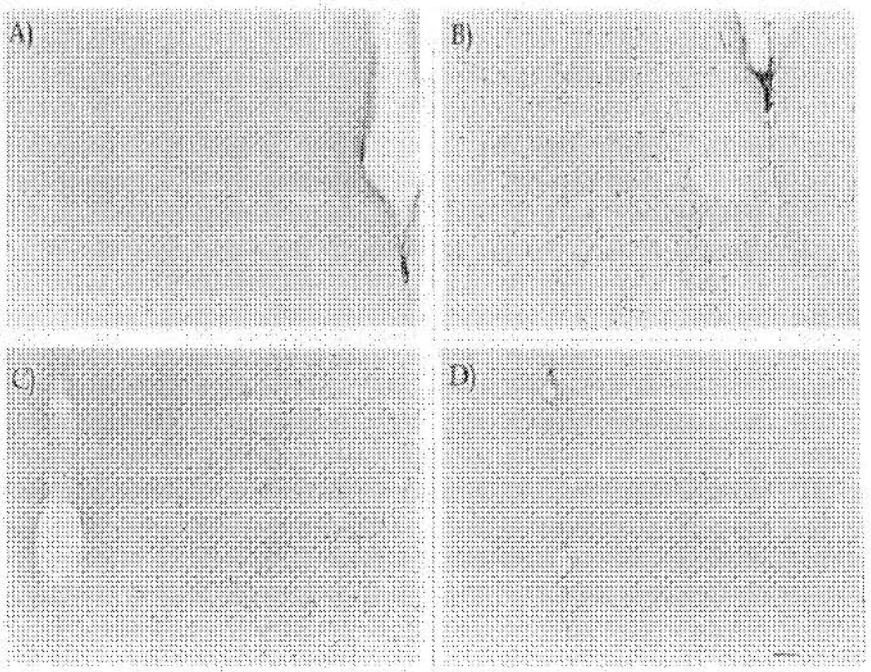
*Indicates significant difference from vehicle group (Kruskal-Wallis test followed by the Mann-Whitney test, $P \leq 0.05$).

FIGURE 33.3. Photomicrographs Showing *Fos*-Like Immunoreactive Neurons in the Dorsal Striatum of Rats Treated I.P. with Vehicle (A), Cannabidiol (120 mg/kg, (B)), Clozapine (20 mg/kg, (C)), or Haloperidol (1 mg/kg, (D))



Note: Bar = 100 µm. (mu/lcm)

FIGURE 33.4. Photomicrographs Showing *Fos*-Like Immunoreactive Neurons in the Prefrontal Cortex of Rats Treated I.P. with Vehicle (A), Cannabidiol (120 mg/kg, (B)), Clozapine (20 mg/kg, (C)), or Haloperidol (1 mg/kg, (D))



Note: Bar = 100 µm. (mu/lcm)

REFERENCES

1. Agurell S, Carlsson S, Lindgreen JE, Ohlsson A, Gillespie H, Hollister L. Interactions of Δ^1-tetrahydrocannabinol with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography. *Experientia* 1981;37(10):1090-1092.

2. Alonso R, Voutsinos B, Fournedier M, Labie C, Steinberg R, Souilhac J, Le Fur G, Soubrie P. Blockade of cannabinoid receptors by SR 141716 selectively increases *Fos* expression in rat mesocorticolimbic areas via reduced dopamine D_2 function. *Neuroscience* 1999;91(2):607-620.

3. Borgen LA, Davis WM. Cannabidiol interaction with tetrahydrocannabinol. *Research Communications in Chemical Pathology and Pharmacology* 1974;7(4):663-670.

4. Bornhein LM, Borys HK, Karler R. Effect of cannabidiol on cytochrome P-450 and hexobarbital sleep time. *Biochemical Pharmacology* 1981;30(5):503-507.

5. Carlini EA, Leite JR, Tanhauser M, Berardi AC. Cannabidiol and *Cannabis sativa* extract protect mice and rats against convulsive agents. *Journal of Pharmacy and Pharmacology* 1973;25(8):664-665.

6. Carlini EA, Santos M, Claussen V, Bieniek D, Korte F. Structure activity relationship of four tetrahydrocannabinols and the pharmacological activity of five semipurified extracts of *Cannabis sativa*. *Psychopharmacologia* 1970;18(7):82-93.

7. Colasanti BK, Brown RE, Craig CR. Ocular hypotension, ocular toxicity and neurotoxicity in response to marihuana extract and cannabidiol. *General Pharmacology* 1984;15(6):479-484.

8. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry and Behavior* 1991;40(3):701-708.

9. Cunha J, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980;21(3):175-185.

10. Dalton WS, Martz R, Lemberger L, Rodda BE, Forney RB. Influence of cannabidiol on Δ^9-tetrahydrocannabinol effects. *Clinical Pharmacology and Therapeutics* 1976;19(3):300-309.

11. Davis WM, Borgen LA. Effects of cannabidiol and Δ^9-tetrahydrocannabinol on operant behavior. *Research Communications in Chemical Pathology and Pharmacology* 1974;9(3):453-462.

12. Fernandes M, Schabarek A, Coper H, Hill R. Modification of Δ^9-THC-actions by cannabinol and cannabidiol in the rats. *Psychopharmacologia* 1974; 38(4):329-338.

13. Grlie L. A comparative study on some chemical and biological characteristics of various samples of cannabis resin. *Bulletin on Narcotics* 1976;14:37-46.

14. Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology* 1990;100(4):558-559.

15. Guimarães FS, de Aguiar JC, Mechoulam R, Breuer A. Anxiolytic effect of cannabidiol derivatives in the elevated plus-maze. *General Pharmacology* 1994; 25(1):161-164.

16. Guimarães FS, Zuardi AW, Graeff FG. Effect of chlorimipramine and maprotiline on experimental anxiety in humans. *Journal of Psychopharmacology* 1987; 1:184-192.

17. Hampson AJ, Grimaldi M, Axelroad J, Wink D. Cannabidiol and (-)Δ^9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95(14):8268-8273.

18. Hetem LA, de Souza CJ, Guimarães FS, Zuardi AW, Graeff FG. Effect of d-fenfluramine on human experimental anxiety. *Psychopharmacology* 1996;127:276-282.

19. Hinderk M, Emrich F, Leweke M, Schneider U. Towards a cannabinoid hypothesis of schizophrenia: Cognitive impairments due to dysregulation of the endogenous cannabinoid system. *Pharmacology, Biochemistry and Behavior* 1997; 56(4):803-807.

20. Hollister LE, Gillespie H. Interactions in man of Δ^9-tetrahydrocannabinol. II. Cannabinol and cannabidiol. *Clinical Pharmacology and Therapeutics* 1975;18(1): 80-83.

21. Howlett AC, Evans D, Houston DB. The cannabinoid receptor. In Murphy L, Bartke A, eds. *Marijuana/cannabinoids: Neurobiology and neurophysiology*. Boca Raton, FL: CRC Press, 1992, pp. 35-72.

22. Izquierdo I, Orshinger OA, Berardi AC. Effect of cannabidiol and other *Cannabis sativa* compounds on hippocampal seizures discharges. *Psychopharmacology* 1973;28(1):95-102.

23. Jones G, Pertwee RG. A metabolic interaction in vivo between cannabidiol and Δ^9-tetrahydrocannabinol. *British Journal of Pharmacology* 1972;45(2):375-377.

24. Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and Δ^9-tetrahydrocannabinol. *Psychopharmacologia* 1973;33(1):53-70.

25. Karniol IG, Shirakawa I, Kasinsky N, Pfeferman A, Carlini E. Cannabidiol interferes with the effect of Δ^9-tetrahydrocannabinol in man. *European Journal of Pharmacology* 1974;28(1):172-177.

26. Kubena RK, Barry III H. Stimulus characteristics of marihuana components. *Nature* 1972;235(5338):397-398.

27. Mincis M, Pfeferman A, Guimarães RX, Ramos OL, Zukerman E, Karniol IG, Carlini EA. Administração crônica de cannabidiol em seres humanos [Chronic administration of cannabidiol in human beings]. *Revista da Associação Médica Brasileira* 1973;19(5):185-190.

28. Monti JM. Hypnoticlike effects of cannabidiol in the rats. *Psychopharmacology* 1977;55(3):263-265

29. Morgan JI, Curran T. Proto-oncogenes: Beyond second messengers. In Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The fourth generation of progress*. New York: Raven Press, 1995, pp. 631-642.

30. Musty RE, Conti LH, Mechoulam R. Anxiolytic properties of cannabidiol. In Harvey DJ, ed. *Marihuana '84. Proceedings of the Oxford Symposium on Cannabis*. Oxford: IRL Press Limited, 1984, pp. 713-719.

31. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. *Journal of Pharmacology and Experimental Therapeutics* 1990;253(3):1002-1009.

32. Paton WDM, Pertwee RG. Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. *British Journal of Pharmacology* 1972;44(2):250-261.

33. Petit F, Jeantaud B, Reibaud M, Imperato A, Dubroeucq MC. Complex pharmacology of natural cannabinoids: Evidence for partial agonist activity of delta(9)-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life Sciences* 1998;63:1-6.

34. Pickens, JT. Sedative activity of cannabis in relation to its Δ^9-tetrahydrocannabinol and cannabidiol content. *British Journal of Pharmacology* 1981;72(4):649-656.

35. Robertson GS, Fibiger HC. Neuroleptics increase *c-fos* expression in the forebrain: Contrasting effects of haloperidol and clozapine. *Neuroscience* 1992; 46(2):315-328.

36. Silveira Filho NG, Tufik S. Comparative effects between cannabidiol and diazepam on neophobia, food intake and conflict behavior. *Research Communication in Psychology, Psychiatry and Behavior* 1981;6:25-26.

37. Silveira MCL, Sandner G, Graeff FG. Induction of *Fos* immunoreactivity in the brain by exposure to the elevated plus-maze. *Behavioural Brain Research* 1993; 56(1):115-118.

38. Thomas BF, Gilliam AF, Burcj DF, Roche MJ, Seltzman HH. Comparative receptor binding analyses of cannabinoid agonists and antagonists. *Journal of Pharmacology and Experimental Therapeutics* 1998;285(1):285-292.

39. Zuardi AW, Antunes-Rodrigues J, Cunha JM. Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacology* 1991; 104(2):260-264.

40. Zuardi AW, Cosme RA, Graeff FG, Guimarães FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of Psychopharmacology* 1993;7:82-88.

41. Zuardi AW, Finkelfarb E, Bueno OFA, Musty RE, Karniol IG. Characteristics of the stimulus produced by the mixture of cannabidiol with Δ^9-tetrahydrocannabinol. *Archives Internationales de Pharmacodynamie et de Therapie* 1981;249(1):137-146.

42. Zuardi AW, Guimarães FS, Moreira AC. Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. *Brazilian Journal of Medical and Biological Research* 1993;26(2):213-217.

43. Zuardi AW, Karniol IG. Changes in the conditioned emotional response of rats induced by Δ^9-THC, CBD and mixture of the two cannabinoids. *Arquivos de Biologia e Tecnologia* 1983;26:391-397.

44. Zuardi AW, Morais SL, Guimarães FS, Mechoulam R. Antipsychotic effect of cannabidiol. *Journal of Clinical Psychiatry* 1995;56(10):485-486.

45. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol I. Action of cannabidiol on the anxiety and other effects produced by Δ^9-THC in normal subjects. *Psychopharmacology* 1982;76(3):245-250.

46. Zuardi AW, Teixeira NA, Karniol IG. Pharmacological interaction of the effects of Δ^9-tetrahydrocannabinol and cannabidiol on serum corticosterone levels in rats. *Archives Internationales de Pharmacodynamie et de Therapie* 1984;269(1): 12-19.

Chapter 34

Anandamides: Potential Glaucoma Medicine?

David W. Pate

The pharmacological action of anandamides closely resembles that of THC in a variety of screening tests specific for psychoactive cannabinoids.[4,5,25,32] Both THC[24] and anandamide[34] also seem to share a common biphasic stimulation-sedation course, reflecting the initially lesser and eventually greater amounts of drug available after administration.[5,15] In addition, THC and anandamide can be mutually antagonistic at very low doses,[6] indicating receptor-site competition, and exhibiting cross-tolerance.[26]

Although the ophthalmic properties of both botanically derived and synthetic cannabinoids have received considerable attention, an investigation of anandamide's possible influence on ocular physiology remains to be conducted. It was thought that elucidation of the relationships between specific synthetic anandamide structures and their intraocular pressure (IOP) action profiles might lead to a new class of topical agents that would be useful for the treatment of the ocular hypertension symptomatic of glaucoma. It was also hoped that such exploration would establish the plausibility of our hypothesis that endogenous anandamide, interacting with a specific cannabinoid receptor of the eye, is involved in the regulation of IOP.

Systemic delivery of THC for the control of ocular hypertension has the disadvantage of psychoactive side effects, which are usually considered acceptable only in cases of last resort. Although anandamide is an endogenous ligand for the CB_1 receptor, topical administration of very small doses to the eye was anticipated to circumvent potential psychoactivity yet provide IOP effects similar to THC. Problems of aqueous insolubility and a unique chemical lability were solved through the application of cyclodextrin technology. This resulted in an increase of anandamide water solubility from nanograms to milligrams, per milliliter, and an improved aqueous solution half-life from hours to years.[8,9]

CYCLODEXTRIN STRUCTURE AND FUNCTION

Cyclodextrins (CDs) are macrocyclic oligosaccharides (see Figure 34.1A) that form three basic ring sizes: *alpha* (α), *beta* (β), and *gamma* (γ), which result from the linkage of either 6, 7, or 8 D-(+)-glucopyranose subunits, respectively. Each has varying inclusion capabilities that stem from differences in their internal cavity dimensions.[7,17]

All hydrophilic hydroxy groups are located on the outside of these structures and their insides are relatively hydrophobic. Through this molecular configuration, cyclodextrins can serve as a water soluble "host" torus (see Figure 34.1B) into which a fatty anandamide "guest" molecule can be introduced to form an "inclusion complex." This complex is not a static entity, but a dynamic relationship between host and guest, and consists of the free drug, the drug-CD complex and unoccupied CD in an equilibrium that is dependent on several factors.[7]

CDs serve as excipients, but cannot be considered passive "fillers," as they are actively involved in the overall effect of the preparation. They function to simultaneously improve drug solubility, stability, dissolution, and bioavailability.[13] Due to the size of these macromolecules, penetration of the cornea does not occur, and because the drug is available for biological interaction only when released from the drug-CD complex (see Figure 34.2), irritation of ocular tissues by the drug is decreased.[13] This latter consideration is particularly critical for the topical delivery of a drug to the eye.

FIGURE 34.1. Structure (A) and Functional Form (B) of β-Cyclodextrin

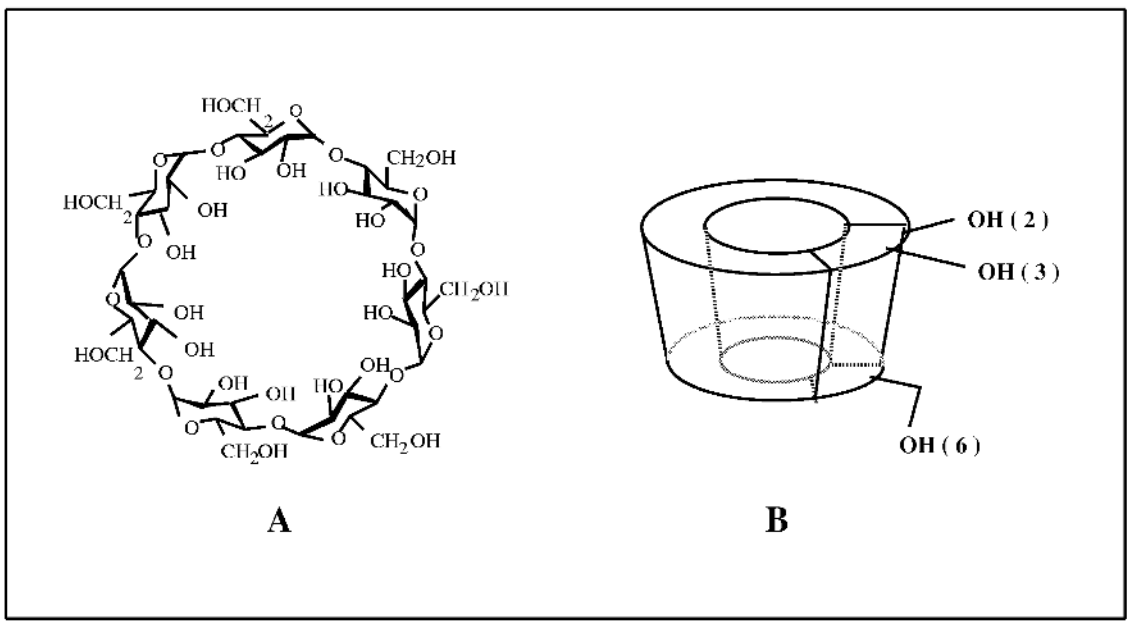
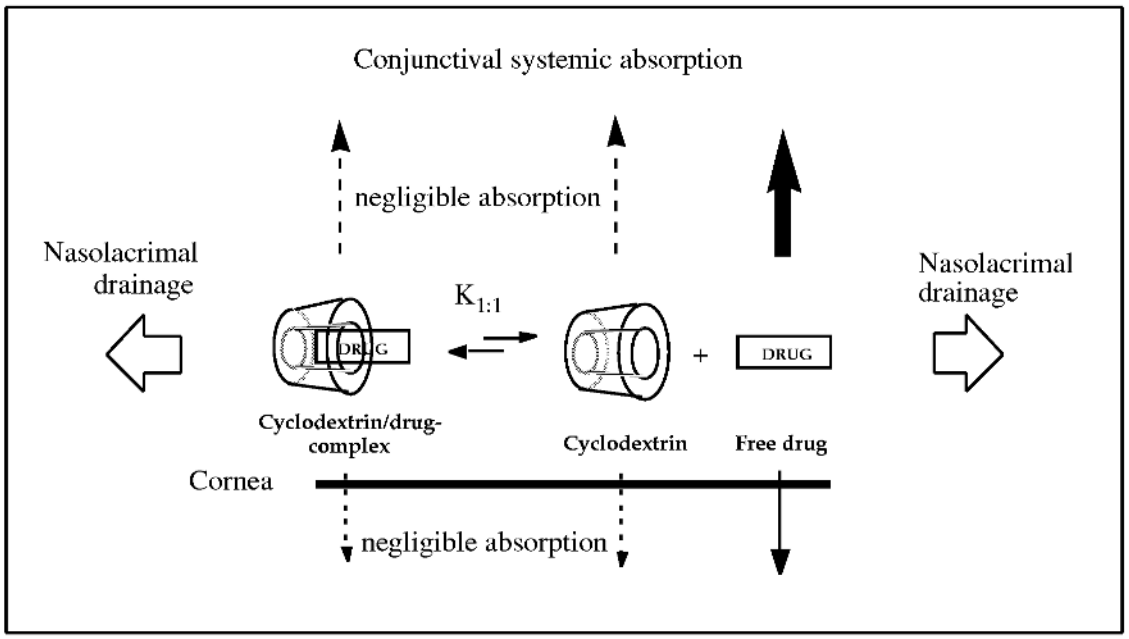


FIGURE 34.2. Drug/Cyclodextrin/Ocular Dynamics



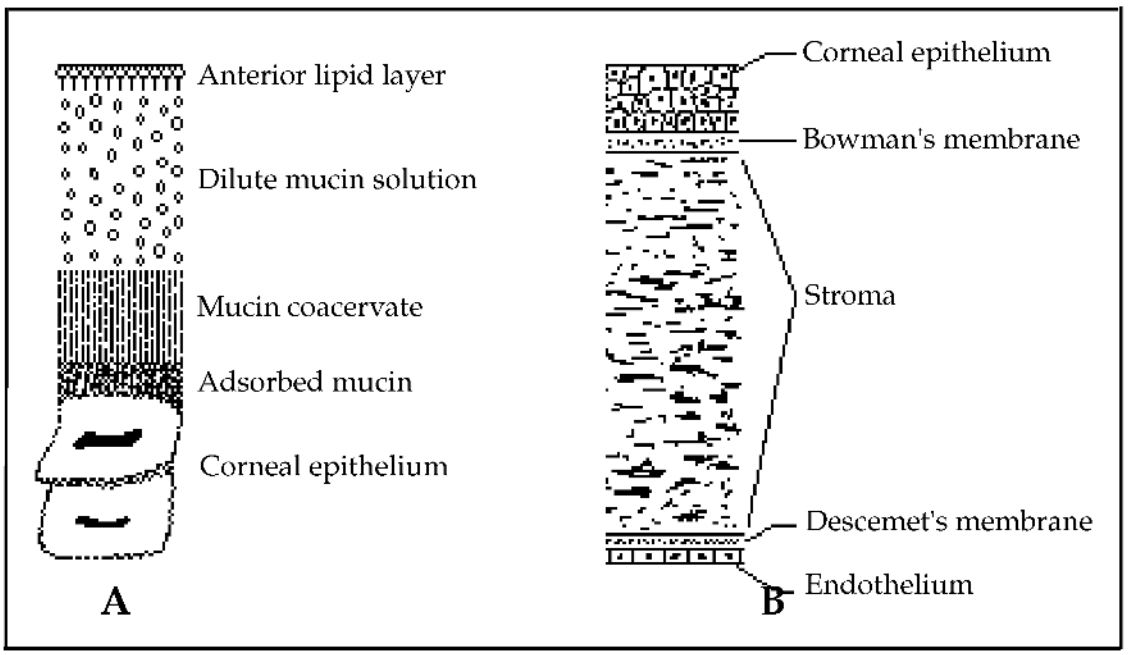
Source: Jarho P. Cyclodextrins in eyedrop formulations: Studies with pilocarpine prodrugs, anandamide and dipivefrine. PhD dissertation, Kuopio University Publications A. Pharmaceutical Sciences 29, 1997.

OCULAR DRUG DELIVERY BARRIERS

The eye is a particularly attractive target organ for the topical application of drugs.[29] It is immediately accessible to both doctor and patient and can be dosed by the noninvasive application of an eyedrop. The surface of the eye (see Figure 34.3A) is constantly bathed with a trilaminate film (35 to 45 µm) of tears. The 1 mm thick cornea (see Figure 34.3B) is composed of five discrete layers, two or three of which can pose significant barriers to drug penetration. The outermost epithelial layer, which is lipophilic, is composed of several cell layers totalling approximately 75 µm in thickness, with intercellular tight junctions at its outermost layers. This poses a considerable barrier for hydrophilic drugs such as pilocarpine,[31] but greatly favors lipophilic drugs (e.g., cannabinoids).

After passing through the epithelium of the eye, and then the thin Bowman's membrane, a drug encounters the aqueous stromal layer, which is a meshwork of highly ordered collagen fibrils comprising 90 percent of corneal thickness. For lipophilic drugs, this layer poses the major rate-limiting barrier, accounting for approximately 50 percent of corneal penetration resistance.[30] From there, the drug may finally enter the aqueous humor only after passing through the relatively permeable Descemet's membrane, and then the endothelium. This last cell monolayer maintains corneal clarity by

FIGURE 34.3. Layers of (A) Tear Film and (B) Cornea



Source: (A) Robinson JC. Ocular anatomy and physiology relevant to ocular drug delivery. In Mitra AK, ed. *Ophthalmic Drug Delivery Systems.* New York: Marcel Dekker, 1993, pp. 29-57. (B) Mitra AK. Ophthalmic drug delivery devices. In Tyle P, ed. *Drug Delivery Devices.* New York: Marcel Dekker, 1988, pp. 467-470.

regulating corneal hydration, which may explain the reversible corneal opacities inducible by chronic topical THC,[3] having only slight barrier properties for hydrophilic drugs.[31] However, it can pose a significant barrier to lipophilic drugs, accounting for up to 50 percent of corneal penetration resistance.[30]

INTRAOCULAR PRESSURE STUDIES

Unilateral ophthalmic administration of arachidonylethanolamide (AEA),[19] or most of its active α-unsubstituted analogues,[20] to normotensive rabbits caused several hours of ocular hypotension preceded by an initial period of hypertension with higher doses, but only a weak response in the contralateral eye. However, the IOP profiles of α-substituted anandamides lacked this initial increase of IOP,[21] and were accompanied by a significant contralateral eye response. This antihypertensive influence increased with the steric bulk of the α-substituent, to a maximum for the isopropyl group.

Subcutaneous indomethacin prevented the IOP effects of AEA,[20] but did not inhibit these effects for *(R)*-α-isopropyl anandamide.[21] The ocular hypotensive effect of a potent CB_1 receptor agonist, CP-55,940, was counteracted by subcutaneous pretreatment with SR 141716A.[22] Such a blockade of *(R)*-α-isopropyl anandamide effects was also demonstrated. However, in marked contrast, the ocular effects of AEA were unaffected. Subcutaneous SR 141716A, also caused an equal bilateral increase of IOP in both undosed eyes of control rabbits.

MECHANISMS OF ACTION

The means by which AEA produces its effects in the rabbit eye was unclear at the onset of these studies, although the phenomenon has since been verified by the work of Mikawa et al.[16] It seems likely that at least the initial hypertensive phase of α-unsubstituted anandamides results from their catabolism to arachidonic acid by ocular amidases[14] or nonspecific esterases.[11] This fatty acid product can then be utilized as a metabolic precursor[27,28] for the biosynthesis of prostaglandins or other products of cyclooxygenase (COX-1), the former of which provoke a characteristic biphasic IOP profile.[12]

The observed asymmetry of IOP action suggests that the effects of AEA on IOP are local, rather than mediated via the central nervous system. The IOP investigations of Sugrue et al.[33] have also discovered evidence of possible local activity, as well as enantioselectivity, for CP-55,940 and other CB_1 receptor ligands. Unilateral administration of α-substituted anandamides provoked a contralateral IOP difference that was less pronounced than that of the α-unsubstituted compounds, which suggests that the former analogues better resist catabolism[1,2] and, therefore, do not serve as arachidonic acid precursors. This contention is supported by the fact that the IOP effects of a large dose of AEA are neutralized by subcutaneous pretreatment with indomethacin, an inhibitor of the COX-1 metabolic pathway. In contrast, the ocular hypotension induced by *(R)*-α-isopropyl anandamide is not affected.[21]

The results obtained by utilizing SR 141716A, a highly specific CB_1 receptor antagonist, imply that this receptor is involved in the IOP reduction induced by either CP-55,940 or *(R)*-α-isopropyl anandamide. The ocular hypertension observed, when this antagonist was subcutaneously administered in conjunction with the ophthalmic control vehicle, indicates either a direct receptor blockade of endogenous AEA, or possibly an inverse agonist mechanism.[18] The lack of influence by SR 141716A on topical AEA effects would seem to further demonstrate this particular anandamide to function through a means separate from that of other cannabinoids. However, recent studies[10] have shown that topical AEA catabolism and consequent COX-1

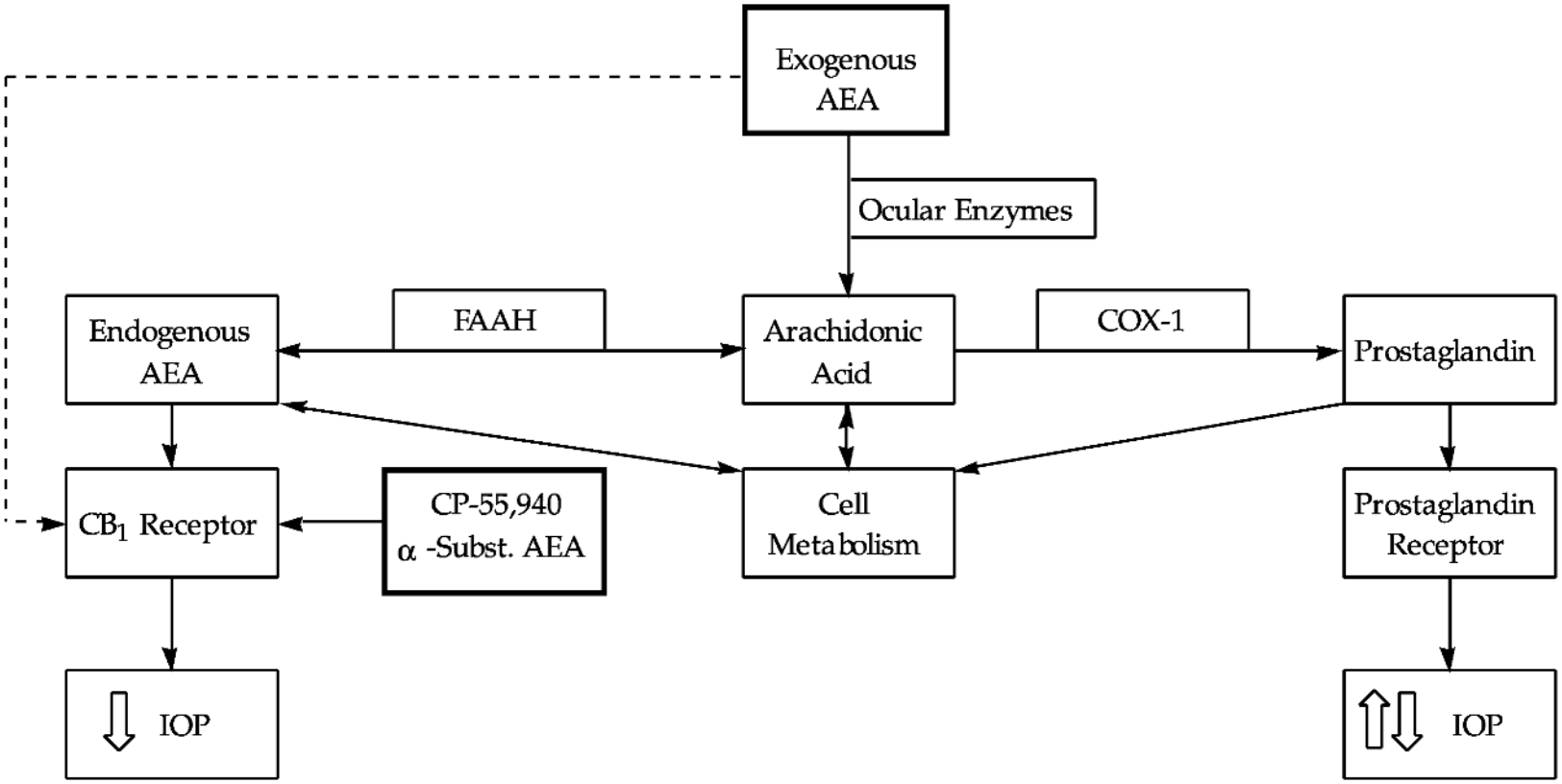
biosynthesis are probably artifacts of the exogenous dose, which is massive and uncontrolled relative to endogenous circumstances.

An overall scheme of ocular anandamide metabolism and IOP dynamics, theorized from our studies,[23] is presented in Figure 34.4.

CONCLUSIONS

These experiments demonstrate that modification of anandamide's molecular structure influences both its topical IOP action profile and the mechanism by which this is achieved. Cannabinoids, including the α-substituted anandamides, seem to affect IOP through a CB_1 receptor mechanism. Of course, the native species of anandamide is AEA, whose influence on IOP is probably more subtle than can be demonstrated by means of a simple exogenous application. Undoubtedly, future experiments of a more sophisticated nature will fully reveal the ocular role of endogenous AEA and the mechanism by which it influences IOP.

FIGURE 34.4. Scheme of Ocular Anandamide Metabolism and IOP Dynamics



REFERENCES

1. Abadji V, Lin S, Gihan T, Griffen G, Stevenson LA, Pertwee GR, Makriyannis A. (*R*)-Methanandamide: A chiral novel anandamide possessing higher potency and metabolic stability. *Journal of Medicinal Chemistry* 1994; 37(12):1889-1893.

2. Adams IR, Ryan W, Singer M, Razdan RK, Compton DR, Martin BR. Pharmacological and behavioral evaluation of alkylated anandamide analogs. *Life Sciences* 1995;56(23-24):2041-2048.

3. Colasanti BK, Powell SR, Craig CR. Intraocular pressure, ocular toxicity and neurotoxicity after administration of Δ^9-tetrahydrocannabinol or cannabichromene. *Experimental Eye Research* 1984;38(1):63-71.

4. Crawley JN, Corwin RL, Robinson JK, Felder CC, Devane WA, Axelrod J. Anandamide, an endogenous ligand of the cannabinoid receptor, induces hypomotility and hypothermia in vivo in rodents. *Pharmacology, Biochemistry and Behavior* 1993;46(4):967-972.

5. Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. *European Journal of Pharmacology* 1993;231(2):313-314.

6. Fride E, Barg J, Levy R, Saya D, Heldman E, Mechoulam R, Vogel Z. Low doses of anandamides inhibit pharmacological effects of delta-9-tetrahydrocannabinol. *Journal of Pharmacology and Experimental Therapeutics* 1995;272(2):699-707.

7. Frömming K-H, Szejtli J. *Cyclodextrins in pharmacy*. Dordrecht, Netherlands: Kluwer Academic Publishers, 1994.

8. Jarho P. Cyclodextrins in eyedrop formulations: Studies with pilocarpine prodrugs, anandamide and dipivefrine. PhD Diss, Kuopio University Publications A. Pharmaceutical Sciences 29, 1997.

9. Jarho P, Urtti A, Järvinen K, Pate DW, Järvinen T. Hydroxypropyl-β-cyclodextrin increases aqueous solubility and stability of anandamide. *Life Sciences* 1996;58(10):181-185.

10. Laine K, Järvinen K, Pate DW, Urtti A, Järvinen T. Phenylmethylsulfonyl fluoride, and its administration with SR 141716A, affects topical anandamide-induced alteration of intraocular pressure in normotensive rabbits. *Journal of Pharmacology and Experimental Therapeutics* (submitted), 2000.

11. Lee H-L, Morimoto KW, Stratford RE. Esterase distribution in the rabbit cornea and its implications in ocular drug bioavailability. *Biopharmaceutics and Drug Disposition* 1982;3(4):291-300.

12. Lee P, Podos SM, Severin C. Effect of prostaglandin $F2_\alpha$ on aqueous humor dynamics of rabbit, cat, and monkey. *Investigative Ophthalmology and Visual Science* 1984;25(9):1087-1093.

13. Loftsson T, Järvinen T. Cyclodextrins in ophthalmic drug delivery. *Advanced Drug Delivery Reviews* 1999;36:59-79.

14. Matsuda S, Kanemitsu N, Nakamura A, Mimura Y, Ueda N, Kurahashi Y, Yamamoto S. Metabolism of anandamide, an endogenous cannabinoid receptor ligand, in porcine ocular tissues. *Experimental Eye Research* 1997;64(5):707-711.

15. Mechoulam R, Ben-Shabat S, Hanus L, Fride E, Vogel Z, Baywitch M, Sulcova AE. Endogenous cannabinoid ligands-chemical and biological studies. *Journal of Lipid Mediators and Cell Signalling* 1996;14(1-3):45-49.

16. Mikawa Y, Matsuda S, Kanagawa T, Tajika T, Ueda N, Mimura Y. Ocular activity of topically administered anandamide in the rabbit. *Japanese Journal of Ophthalmology* 1997;41(4):217-220.

17. Mitra AK. Ophthalmic drug delivery devices. In Tyle P, ed. *Drug delivery devices*. New York: Marcel Dekker, 1988, pp. 456-470.

18. Pan X, Ikeda SR, Lewis DL. SR 141716A acts as an inverse agonist to increase neuronal voltage-dependent Ca^{2+} currents by reversal of tonic CB_1 cannabinoid receptor activity. *Journal of Pharmacology and Experimental Therapeutics* 1998;54(6):1064-1072.

19. Pate DW, Järvinen K, Urtti A, Jarho P, Järvinen T. Ophthalmic arachidonyl ethanolamide decreases intraocular pressure in normotensive rabbits. *Current Eye Research* 1995;14(9):791-797.

20. Pate DW, Järvinen K, Urtti A, Jarho P, Fich M, Mahadevan V, Järvinen T. Effects of topical anandamides on intraocular pressure in normotensive rabbits. *Life Sciences* 1996;58(21):1849-1860.

21. Pate DW, Järvinen K, Urtti A, Jarho P, Mahadevan V, Järvinen T. Effects of topical *alpha*-substituted anandamides on intraocular pressure in normotensive rabbits. *Pharmaceutical Research* 1997;14(12):1738-1743.

22. Pate DW, Järvinen K, Urtti A, Mahadevan V, Järvinen T. Effect of the CB_1 receptor antagonist, SR 141716A, on cannabinoid-induced ocular hypotension in normotensive rabbits. *Life Sciences* 1998;63(24):2181-2188.

23. Pate DW. Anandamide Structure-Activity Relationships and Mechanisms of Action on Intraocular Pressure in the Normotensive Rabbit Model. PhD Diss, Kuopio University Publications A. Pharmaceutical Sciences 37, 1999.

24. Paton WDM, Pertwee RG. The pharmacology of cannabis in animals. In Mechoulam R, ed. *Marijuana: Chemistry, pharmacology, metabolism, and clinical effects*. New York: Academic Press, 1973, pp. 191-285.

25. Pertwee RG, Stevenson LA, Elrick DB, Mechoulam R, Corbett AD. Inhibitory effects of certain enantiomeric cannabinoids in the mouse vas deferens and the myenteric plexus preparation of guinea pig small intestine. *British Journal of Pharmacology* 1992;105(4):980-984.

26. Pertwee RG, Stevenson LA, Griffen G. Cross-tolerance between delta-9-tetrahydrocannabinol and the cannabimimetic agents, CP-55,940, WIN 55,212-2 and anandamide. *British Journal of Pharmacology* 1993;110:1483-1490.

27. Podos SM, Becker B, Kass MA. Prostaglandin synthesis, inhibition, and intraocular pressure. *Investigative Ophthalmology* 1973;12(6):426-433.

28. Podos SM, Becker B, Kass MA. Indomethacin blocks arachidonic acid-induced elevation of intraocular pressure. *Prostaglandins* 1973;3(1):7-16.

29. Robinson JC. Ocular anatomy and physiology relevant to ocular drug delivery. In Mitra AK, ed. *Ophthalmic Drug Delivery Systems*. New York: Marcel Dekker, 1993, pp. 29-57.

30. Schoenwald RD. Ocular drug delivery. Pharmacokinetic considerations. *Clinical Pharmacokinetics* 1990;18(4):255-269.

31. Sieg JW, Robinson JR. Mechanistic studies on transcorneal permeation of pilocarpine. *Journal of Pharmaceutical Sciences* 1976;65(12):1816-1822.

32. Smith PB, Compton DR, Welch SP, Razdan RJ, Mechoulam R, Martin BR. The pharmacological acivity of anandamide, a putative endogenous cannabinoid, in mice. *Journal of Pharmacology and Experimental Therapeutics* 1994;270(1):219-227.

33. Sugrue MF, Funk HA, Leonard Y, O'Neill-Davis L, Labelle M. The ocular hypotensive effects of synthetic cannabinoids. *Investigative Ophthalmology and Visual Science* 1996;37:831.

34. Sulcova E, Mechoulam R, Fride E. Biphasic effects of anandamide. *Pharmacology, Biochemistry and Behavior* 1998;59(2):347-352.

Chapter 35

Therapeutic Potential of Ajulemic Acid (CT3)

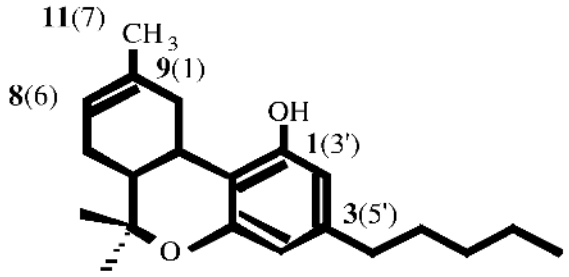
Sumner H. Burstein

BACKGROUND

Delta-8-THC, a highly lipophilic molecule, has a structure that is one of the cannabis constituents responsible for its mood-altering effects (see Figure 35.1). The Δ^9-isomer is much more abundant in the plant; however, the biological effects of the two isomers differ only slightly. Because the Δ^8 series compounds are more easily synthesized, they are the preferred molecules for drug development projects. Both isomers of THC are metabolized rapidly in the body to a number of oxygenated products (see Chapter 6); however, the most important route in humans involves oxidation of the allylic methyl group.[2] Oxidation may also occur elsewhere in the molecule, notably at various positions on the side chain, leading to polyfunctional metabolites. A profound change in the biological activities of these substances accompanies the course of metabolism at the 11 position. Although monohydroxy THC and its aldehyde product have pharmacological profiles similar to THC, the terminal carboxy metabolite has no psychotropic effect in humans,[12] and does not produce some of the behavioral responses in laboratory animals typical of THC.[5] In fact, THC-11-oic acid antagonizes the cataleptic effect of THC in mice[4] by an undetermined mechanism.

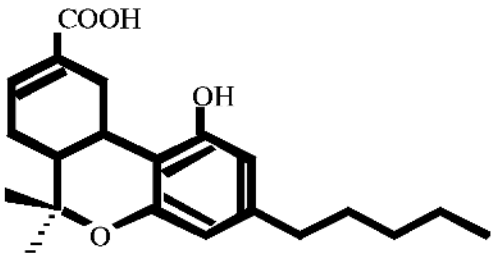
Antagonism by THC-11-oic acid to one of the effects of THC in vitro has also been reported;[3] the acid inhibits THC-induced synthesis of iPGE- (immunoreactive prostaglandin) (Cayman Chemical, personal communication) in WI-38 human lung fibroblasts, probably by inhibiting the action of COX (cyclooxygenase). Inhibition of prostaglandin (PG) synthesis is a typical property of NSAIDs (nonsteroidal anti-inflammatory drugs), and this observation[3] suggests that THC-11-oic acid may exhibit similar effects in experimental models of pain and inflammation. This possibility was tested

FIGURE 35.1. Comparison of the Molecular Structures of THC, THC-11-Oic Acid, and Ajulemic Acid



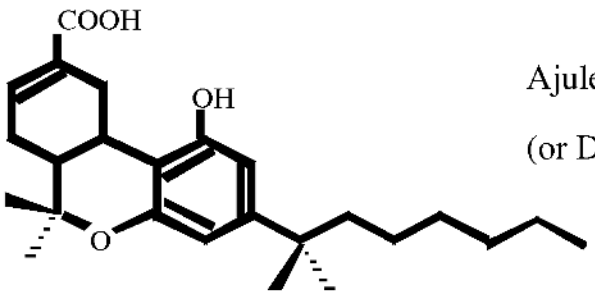
THC (delta 8-tetrahydrocannabinol)

Bold numbers: currently used system.
Bracketed numbers: older system.



THC-11-Oic Acid

(or THC-7-Oic Acid)



Ajulemic Acid (CT3)

(or DMH-THC-11-Oic Acid)

in several animal models in which it was observed that the acid behaved as an NSAID in the mouse hot plate test,[5,10] the PAF (platelet-aggregating factor) and arachidonate-induced paw edema tests,[6] the PPQ (paraphenylquinone) writhing assay,[10] and PAF-induced mortality.[6] These findings raised the possibility that the analgesic and anti-inflammatory properties of THC may, in fact, be due to its acid metabolites.

A comparison of the pharmacokinetics of THC versus THC-11-oic acid for both the mouse hot plate[5] and PAF-induced edema[6] models has been done. In both cases, the acids exhibited earlier and greater analgesic/anti-inflammatory activity. This data is consistent with the idea of metabolic activation of THC, although other explanations such as different degrees of bioavailability for THC and the acid are a possible cause for the more rapid and more robust action of THC-11-oic acid. In the hot plate study, THC ac-

tually caused hyperalgesia at early time points, in contrast to the acid, which was antinociceptive at all time points.[5]

More recently, studies aimed at the therapeutic potential of the cannabinoid acids have taken a somewhat different approach, namely, the use of synthetic analogues of THC-11-oic acid as candidate molecules. These analogues will also, undoubtedly, provide better tools in the search for the sites of action of the acids, in much the same way that the DMH (dimethylheptyl) analogues of THC have proven useful in characterizing the cannabinoid CB_1 receptor. Moreover, it is expected that such acid analogues will provide interesting substances for testing as clinically useful agents free of the psychotropic effects of THC. An example of such an analogue is AJA (1a',1'-dimethylheptyl-THC-11-oic acid; ajulemic acid) shown in Figure 35.1. Modification of the pentyl side chain in THC can produce molecules with generally greater potencies.[11] In particular, increasing the chain length to seven carbons and introducing branching close to the ring can lead to compounds with potencies that are 50 to 100 times greater than THC. This strategy was employed in designing the structure of ajulemic acid, and the initial study supported the expectation for its increased potency as an analgesic/anti-inflammatory agent in several models.[7]

Typical properties of NSAIDs apparently not shared by THC-11-oic acid are the major adverse effects of NSAIDs, namely, gastrointestinal and kidney toxicity. This statement is based partly on experimental findings and partly on anecdotal information.[1] THC-11-oic acid given at twice the maximum effective analgesic/anti-inflammatory dose did not cause any lesions under conditions in which aspirin and indomethacin, two common NSAIDs, displayed significant toxicity. This finding is in agreement with an extensive body of anecdotal evidence showing that chronic users of cannabis, who are exposed to high blood levels of this THC metabolite, appear to be free from NSAID-type toxicity. The precise basis for this difference is not well understood; however, it may be due partly to a selective inhibition by THC-11-oic acid for COX-2 versus COX-1. This is supported by the observation that the acid does not affect platelet aggregation, a COX-1-mediated effect (A. Meyers, personal communication). AJA also shows little effect on platelet aggregation,[8] suggesting that it will not produce the toxicities associated with NSAID usage.

These findings suggest strongly that, contrary to long-held beliefs, the acid metabolites of THC are not "inactive" and exhibit a pharmacological profile quite different from THC. As a consequence of these beliefs, very little research has been done on a possible role for these metabolites in the overall effects of cannabis use in humans. However, the acids may not only contribute to the analgesic properties of THC, but could also affect the duration and intensity of the psychotropic effects. For example, one report shows that the prior administration of THC-11-oic acid to mice limits the

cataleptic response to THC.[4] This may be related to the observation that indomethacin, a potent NSAID, antagonizes specific responses to smoked marijuana in humans.[13] If this "metabolite hypothesis" is valid, it could help explain the relatively low toxicity associated with THC since the agonist would generate its own antagonist during the course of metabolism.

STEREOSPECIFICITY

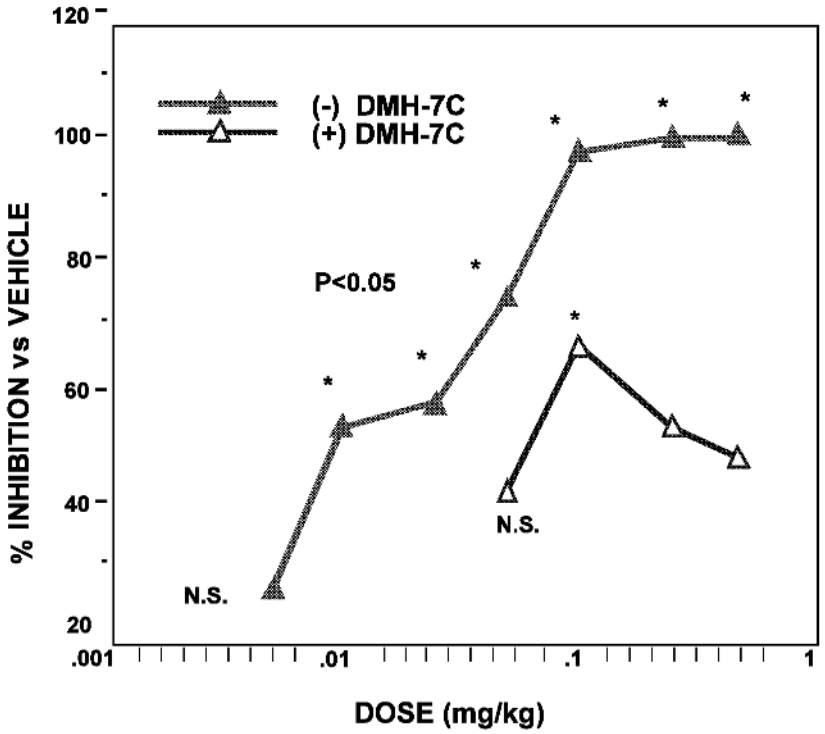
AJA and its S,S enantiomer have been directly compared for stereospecificity of action.[7] A high degree of specificity was shown in the mouse paw edema assay with AJA being much more potent (see Figure 35.2). In fact, the modest response shown by enantio AJA is likely due to a 5 percent contamination with AJA. It is interesting to note that enantio AJA is a likely metabolite of the drug dexanabinol (see Chapter 36). It would be of interest to see whether some of the in vivo actions of dexanabinol might be due to its biotransformation to enantio AJA. These observations on stereospecificity suggest that at least some of the actions of AJA are receptor mediated.

CANNABINOID ACIDS DO NOT BIND TO CB_1 OR CB_2

Consistent with their low psychotropic activity, the cannabinoid acids have recently been reported to exhibit only weak binding to either CB_1 or CB_2.[9,14,15] Data are presented in modified form in Table 35.1. A striking decrease in potency is apparent across the board when AJA is compared with DMH-THC both for binding and inhibition of adenylate cyclase. THC itself generally shows greater activity than AJA with one minor exception: binding to CB_1 in transfected cells. Thus, at therapeutic doses, it appears that the cannabinoid acids act at a site (or sites) other than CB_1 or CB_2.

Given the potency and specificity of AJA as an analgesic and anti-inflammatory agent, it seems very likely that it would display binding to one or more tissue sites. To quote Paul Ehrlich, "Corpora non agunt nisi fixata" [Substances cannot function unless they are bound]. Recent reports[14,15] all but eliminate either CB_1 or CB_2 as candidate receptors suggesting that there must be other sites where the cannabinoid acids bind in order to express their pharmacological actions. It is entirely possible that CB receptors other than CB_1 or CB_2 may exist and that the acids may show high affinity and specificity for one of these. Moreover, it is also possible that they may bind to macromolecules involved in the arachidonic acid cascade such as the cyclooxygenases or lipoxygenases, as well as other enzymic mediators or ion channels. Such binding sites may not have been detected using the currently available radiolabelled probes since they very likely have different ligand specificities.

FIGURE 35.2. Stereospecificity of Ajulemic Acid in Arachidonic Acid-Induced Paw Edema



Note: *Significant changes in paw volume; N.S. = Not significant. Arachidonic acid (1.0 mg) dissolved in 50 µl of 5 percent ethanol in saline was injected s.c. into the plantar surface of the right hind paw of CD-1 female mice (20-25 g) obtained from Charles River Labs. The volume of the right foot was measured to the level of the lateral malleolus by water displacement before treatment and 30 min after arachidonate injection. The change in paw volume was calculated for each mouse and the significance for each group was determined by a paired t test analysis. A subsequent analysis for chiral purity by hplc (Chiracel OD-R) showed that while (-) ajulemic acid (CT3) was essentially the pure R,R enantiomer, (+) ajulemic acid, the S,S enantiomer, contained 5 percent contamination of the R,R isomer (S. Abidi, personal communication). This suggests a much higher degree of stereospecificity for AJA than indicated by the data shown. DMH-7C = ajulemic acid; (+) DMH-7C= enantio AJA.

ANTI-INFLAMMATORY EFFECTS OF AJULEMIC ACID

The anti-inflammatory activity of AJA was studied in animal models of acute and chronic inflammation.[16] Oral administration of AJA reduced the accumulation of pouch fluid leukocytes in the mouse subcutaneous air pouch model of acute inflammation and reduced significantly the severity

TABLE 35.1. Relative Binding (KI) and Functional Activities (EC_{50}) of Ajulemic Acid Compared with THC

	Binding			Adenylate cyclase	
	Brain	CB_1	CB_2	CB_1	CB_2
THC	1.00*	1.21	0.48	1.00*	>90
DMH-THC	0.04	0.004	0.003	0.053	0.092
Ajulemic acid	7.23	0.49	2.56	84.3	10.6

Source: Adapted from Rhee MH, Vogel Z, Barg J, Bayewitch M, Levy R, Hanus L, Breuer R, Mechoulam R. Cannabinol derivatives: Binding to cannabinoid receptors and inhibition of adenylylcyclase. *Journal of Medicinal Chemistry* 1997;40(20):3228-3233.

* K1 = 66.5 ± 5.8 nM
**EC-50 = 11.0 ± 2.1nM (inhibition of forskolin-stimulated adenylate cyclase)

of adjuvant-induced polyarthritis in rats. The subcutaneous air pouch simulates a synovial cavity, and the adjuvant arthritis model has been used extensively to evaluate anti-inflammatory and immunosuppressive drugs. Histopathologic studies showed that ajulemic acid treatment attenuated joint tissue inflammation and injury in the arthritis model. Thus, joint cartilage and bone damage was prevented by ajulemic acid treatment. The animals did not exhibit evidence of tolerance to ajulemic acid during the 30 days of treatment; tolerance is a hallmark of the psychotropic group of cannabinoids. This observation indicates a clear divergence in the mechanism of action between the cannabinoid acids and other cannabinoids.

ANALGESIC EFFECTS OF AJULEMIC ACID

Results of studies to further characterize the analgesic potential of ajulemic acid indicate that the analogue reduces markedly the behavioral responses to painful stimuli.[8] In the PPQ writhing assay in the mouse, AJA (0.2 to 10 mg/kg i.v.) completely reduced the writhing response with an ID-50 at 1.24 mg/kg. In the mouse formalin antinociception test, a 64 percent reduction in the early phase response and a 48 percent reduction in the late phase response was observed at a dose of 4.64 mg/kg i.v. using

three behavioral measures for activity. This differs from a typical NSAID response in which only a late-phase effect would be expected. Under these conditions, motor function was not altered in the rota rod procedure. Hot plate assays were done at two surface temperatures, 48°C and 58°C, to provide some insight into the mechanism of the antinociceptive activity of AJA. A significant decrease in potency was seen at the higher temperature, an effect that is considered characteristic of nonopiate-mediated action.

As reported for THC-11-oic acid,[4] the DMH analogue did not produce a cataleptic response in the mouse as measured by the ring test. Moreover, AJA significantly antagonized, in a dose-related manner, THC-induced catalepsy in the same model. The mechanism for this observed antagonism is a matter for speculation at this time. However, it seems improbable that the acids act directly on the ligand binding site of the CB_1 receptor. Since THC-induced catalepsy is thought to be mediated by the CB_1 receptor, it seems more likely that antagonism by the acids may involve the inhibition of a downstream process following receptor-ligand interaction. There may even be some features in common with the analgesic/anti-inflammatory effects of the acids, for example, an inhibition of eicosanoid synthesis.

FUTURE DIRECTIONS

AJA has recently been approved for a Phase 1 trial in humans for application as an acute orally administered analgesic (P. Schalk, personal communication). Based on the preclinical studies and the low toxicity of cannabinoids in general, no adverse reactions including psychotoxicity are expected at therapeutic doses. In unrelated studies, AJA appears to have potent anticancer effects in both in vitro and in vivo models (L. Recht, personal communication). This is not entirely unexpected in view of recent reports suggesting that NSAIDs may be efficacious in both the treatment and prevention of certain cancers.

REFERENCES

1. Burstein SH. The cannabinoid acids: Nonpsychoactive derivatives with therapeutic potential. *Pharmacology and Therapeutics* 1999;82(1):87-96.

2. Burstein S, Rosenfeld J, Wittstruck T. Isolation and characterization of two major urinary metabolites of Δ^1-tetrahydrocannabinol. *Science* 1972;176:422-423.

3. Burstein S, Hunter SA, Latham V, Renzulli L. Prostaglandins and cannabis XVI. Antagonism of Δ^1-THC action by its metabolites. *Biochemical Pharmacology* 1986;35:2553-2558.

4. Burstein S, Hunter, SA, Latham V, Renzulli L. A major metabolite of Δ^1-THC reduces its cataleptic effect in mice. *Experientia* 1987;43(4):402-403.

5. Burstein SH, Hull K, Hunter SA, Latham V. Cannabinoids and pain responses: A possible role for prostaglandins. *FASEB Journal* 1988;2(14):3022-3026.

6. Burstein SH, Audette CA, Doyle SA, Hull K, Hunter SA, Latham V. Antagonism to the actions of PAF by a nonpsychoactive cannabinoid. *Journal of Pharmacology and Experimental Therapeutics* 1989;251(2):531-535.

7. Burstein SH, Audette CA, Breuer A, Devane WA, Colodner S, Doyle SA, Mechoulam R. Synthetic nonpsychotropic cannabinoids with potent anti-inflammatory, analgesic and leukocyte anti-adhesion activities. *Journal of Medicinal Chemistry* 1992;35(17):3135-3141.

8. Burstein SH, Friderichs E, Kogel B, Schneider B, Selve N. Analgesic effects of 1',1' Dimethylheptyl-Δ^8-THC-11-oic Acid (CT3) in mice. *Life Sciences* 1998; 63(3):161-168.

9. Compton DR, Rice KC, De Costa BR, Razdan RK, Melvin LS, Johnson MR, Martin BR. Cannabinoid structure-activity relationships: Correlation of receptor binding and in vivo activities. *Journal of Pharmacology and Experimental Therapeutics* 1993;265(1):218-226.

10. Doyle SA, Burstein SH, Dewey WL, Welch SP. Further studies on the antinociceptive effects of Δ^6-THC-7-oic acid. *Agents and Actions* 1990;31(1-2):157-162.

11. Loev B, Bender PE, Dowalo F, Macko E, Fowler PJ. Cannabinoids: Structure-activity studies related to 1,2-dimethylheptyl derivatives. *Journal of Medicinal Chemistry* 1973;16(11):1200-1206.

12. Perez-Reyes M. Pharmacodynamics of certain drugs of abuse. In Barnett G, Chiang NC, eds. *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs*. Foster City, CA: Biomedical Publishers, 1985.

13. Perez-Reyes M, Burstein SH, White WR, McDonald SA, Hicks RE. Antagonism of marijuana effects by indomethacin. *Life Sciences* 1991;48(6):507-515.

14. Rhee MH, Vogel Z, Barg J, Bayewitch M, Levy R, Hanus L. Breuer R, Mechoulam R. Cannabinol derivatives: Binding to cannabinoid receptors and inhibition of adenylylcyclase. *Journal of Medicinal Chemistry* 1997;40(20):3228-3233.

15. Yamamoto I, Kimura T, Kamei A, Yoshida H, Watanabe K, Ho IK, Yoshimura H. Competitive inhibition of THC and its active metabolites for cannabinoid receptor binding. *Biological and Pharmaceutical Bulletin* 1998;21(4):408-410.

16. Zurier RB, Rossetti RG, Lane JH, Goldberg JM, Hunter SA, Burstein SH. Dimethylheptyl-THC-11-oic acid: A nonpsychoactive anti-inflammatory agent with a cannabinoid template structure. *Arthritis and Rheumatism* 1998;4(1):163-170.

Chapter 36

HU-211: A Cannabinoid Neuroprotective Agent

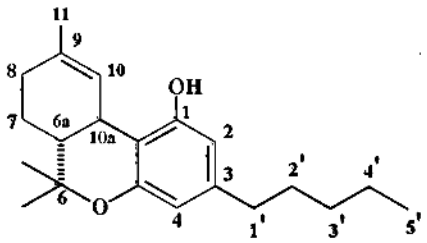
Raphael Mechoulam
Ester Shohami

INTRODUCTION

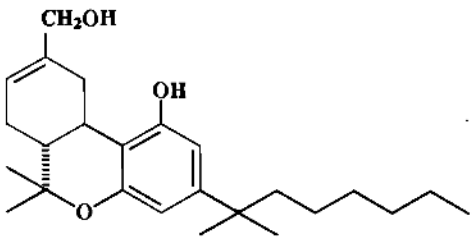
In 1988, in a study on the relationship between stereochemistry (structure in space) and cannabinoid activity, we prepared a highly potent analogue of Δ^8-THC—code numbered HU-210—as well as its enantiomer (mirror image)—code numbered HU-211 (see Figure 36.1).[15,17] HU-210 proved to be the most potent cannabinoid synthesized until then. In various tests in vitro and in vivo, HU-210 was between 80 and 800 times more active than the natural Δ^9-THC, depending on the test employed.[14,16] In contrast, HU-211 did not show any THC-type activity when measured in numerous tests: it did not cause sedation, immobility, reduction of body temperature, etc., even when tested at doses several thousand times higher than the active doses of HU-210.[14,16] However, on administration of relatively high doses of HU-211 to mice, we noted behavior—grooming, rearing, scratching, and licking—which resembled that of antagonists to the glutamate receptor (or more exactly, to the *N*=methyl D=asparate (NMDA) subtype of the glutamate receptor).[8] Glutamate is the principal excitatory transmitter in the brain. It activates several receptor subtypes, one of which is named after the compound *N*-methyl, D-aspartic acid (NMDA) which activates a particular receptor subtype.

Glutamate interactions with specific membrane receptors are responsible for many neurologic functions, including cognition, memory, movement, and sensation. However, in a variety of pathologic conditions, including stroke, trauma, and various neurodegenerative disorders, excessive activation of glutamate receptors may mediate neuronal injury or death[13] (see also Chapter 9).

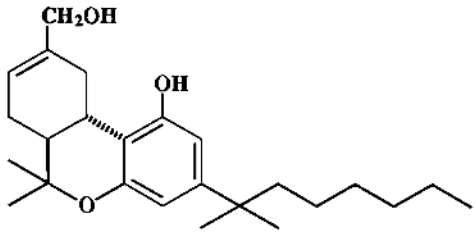
FIGURE 36.1. Chemical Structures of THC, HU-210, and HU-211



Δ^9-tetrahydrocannabinol (Δ^9-THC)



HU-210



HU-211

The initial observations on HU-211, apparently acting as an NMDA antagonist, led us to investigate the effect of HU-211 in mice administered NMDA. This compound, which activates the NMDA subtype of the glutamate receptor, at high doses is a potent poison, presumably causing overactivation of the receptor. We found that subcutaneous administration of 2.5 mg/kg HU-211 blocked the tremorogenic, convulsive, and lethal effects of NMDA (100 mg/kg).[8] Binding studies showed that HU-211 blocks NMDA receptors and that the interaction occurs at binding sites distinct from those of other noncompetitive NMDA antagonists. These initial studies led us to undertake a thorough investigation of the pharmacological properties of HU-211, as in various disease states, as mentioned, there is evidence for involvement of glutamate receptors in neuronal damage.[8]

Lipton and Rosenberg[13] have compiled a list of neurological disorders considered to be mediated, at least in part, through stimulation of glutamate receptors:

1. *Acute neurologic disorders:* strong evidence for involvement in cerebral ischemia, stroke, hypoxia, anoxia, poisoning by carbon monoxide, cyanide, hypoglycemia, and mechanical trauma

2. *Chronic neurodegenerative diseases:* good evidence for involvement in Huntington's disease, AIDS dementia complex, neuropathic pain syndromes, and suggestive evidence for involvement in parkinsonism, amyotrophic lateral sclerosis, as well as various cerebellar atrophies and perhaps Alzheimer's disease

At present, there are no efficient drugs to treat these conditions, as most NMDA antagonists (such as the Merck compound MK 801) investigated so far have been withdrawn from clinical trials due to serious side effects. As the cannabinoids have not shown major side effects, it seems possible that a new drug from this family of compounds may represent a promising new therapeutic agent, in particular since HU-211 does not cause THC-type effects.

IN VITRO EFFECTS OF HU-211

Nadler et al. have investigated the effect of HU-211 on the uptake of radioactive Ca by primary neuronal cultures of rat forebrain, as Ca uptake into cells is a measure of the activity of the NMDA channel. A significant blockage was noted, as expected for an NMDA antagonist.[19]

Nadler et al.[20] and Eshhar et al.[6] have further demonstrated that HU-211, in a dose-dependent manner, can protect neurons against NMDA and glutamate neurotoxicity mediated by NMDA receptors.[20] Although the primary effect of HU-211 is on the glutaminergic system, other beneficial effects were also observed. Eshhar et al. also reported that HU-211 is an effective scavenger of peroxy entities (which cause oxidative damage) in vitro and protects cultured neurons from toxic effects of generators of free radicals. Free radicals are chemical species of high reactivity which may cause substantive damage in the body. As the action of peroxy entities involves free radicals, it is apparent that HU-211 inhibits free radical action and toxicity, including oxidative damage. Primary cerebral cortical cell cultures were also exposed to anoxia, produced by glucose and oxygen deprivation, and HU-211 attenuated neuronal cell damage under these conditions.[7]

Tumor necrosis factor (TNFα) is a protein that is involved in the pathogenesis of various immune-mediated processes: multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, and cachexia (weight loss and wasting). It is a key mediator in the highly dangerous condition of septic shock.[25] Gallily et al. have looked into the effect of HU-211 on TNFα production by macrophages, which are the main producers of this compound in the body. HU-211 was found to markedly suppress TNFα production.[10]

The effects of HU-211 in vitro are summarized in Table 36.1.

TABLE 36.1. Neuroprotective Effects of HU-211 in Vitro

Model	Effect	Reference
Primary neuronal culture	Reduction of NMDA-induced mortality	8,9
Primary neuronal culture	Blockage of NMDA-induced calcium uptake	7
Primary neuronal culture	Rescue of cells from NO-toxicity	10
Primary neuronal culture	Attenuation of effects of oxygen deprivation	10
Macrophages (enhanced TNFα production by lipopolysaccharide)	Marked suppression of TNFα production	12

IN VIVO EFFECTS OF HU-211

As brain trauma, ischemia, and bacterial infection are associated with damage mediated by glutamate, it was important to investigate the effect of HU-211 in relevant experimental animal models.

Closed Head Injury (CHI) in Rats

A model of CHI was used to investigate the potential therapeutic efficacy of HU-211. In this model, a weight-drop device was used to induce CHI in ether-anesthetized male rats. HU-211 was administered intravenously (i.v.) to the experimental animals 1 h after injury. To study the therapeutic window, i.e., the time after damage while the drug is still effective, HU-211 was injected at 1, 4, or 6 h after CHI. The typical parameters that were assessed to define the extent of damage and to evaluate the neuroprotective effect of the drug were: edema (water content), blood-brain barrier (BBB) integrity, clinical status, and memory. These parameters were evaluated for a period of 30 days. HU-211 administered i.v. was very effective at improving cognitive and motor function recovery during the entire evaluation period. It also reduced BBB breakdown and attenuated the development of cerebral edema in the traumatized hemisphere. Hippocampal cells (which are associated with memory) were also protected by HU-211 treatment, and less cell death was observed in important brain regions (named CA_2 and CA_3).[22,23]

To associate this beneficial effect with the proposed mechanism of action of HU-211, namely, the blockade of the NMDA-operated calcium channel, the accumulation of radioactive Ca in various brain regions was determined during the 72 h period after CHI. A significant attenuation of Ca accumulation was indeed demonstrated.[18]

The effect of HU-211 on TNFα production was studied in the same model of CHI. TNF accumulated in the brain after CHI, peaking at 4 h. In HU-211-treated rats, 90 percent inhibition of the TNFα surge was demonstrated, suggesting that HU-211 may exert its cerebroprotective effect by inhibition of the cytokine cascade, in addition to its anti-NMDA effect.[21] The "cytokine cascade" is the consecutive formation of proteins (cytokines) in the body which have a variety of functions. Some cytokines may cause considerable damage.

Based on these results we may conclude that HU-211 is an effective cerebroprotective agent even when given up to 4 h after closed head injury. The beneficial effect obtained even after a single dose is long lasting, and ameliorates impairment of both motor and cognitive functions following CHI.

Models of Cerebral Ischemia

The effect of HU-211 was studied in a number of experimental models of ischemia. Bar-Joseph et al. showed that following 10 min of bilateral, carotid occlusion in Mongolian gerbils, there was a significantly higher cell survival in the hippocampal region associated with memory in animals that received HU-211.[1] Similarly, in a model of severe forebrain ischemia in the rat, Belayev et al. demonstrated significantly more viable neurons in the hippocampus in HU-211-treated rats than in control rats.[3]

Recently, Leker et al. investigated experimental focal cerebral ischemia in a clinical-relevant model (named permanent middle cerebral artery occlusion). HU-211 significantly decreased infarct volumes and lowered TNFα levels.[12]

Belayev et al. also reported that posttraumatic treatment with HU-211 significantly protected the integrity of the BBB. These authors used an experimental model of ischemia in rats injected i.v. with a dye. They found decreased presence of the dye into the area of infarct at 23 h after the onset of ischemia, after treatment with HU-211.[4]

Experimental Pneumococcal Meningitis

Antibacterial therapy of meningitis, which aims at killing the bacteria, does not offer a full cure for the disease, as mediators released during bacteriolysis are also harmful and may trigger secondary, devastating damage. In a search for adjuvant therapy to experimental meningitis in the rat,

Bass and colleagues treated rats, infected with *Streptococcus pneumoniae,* with HU-211 in addition to the antibiotic ceftriaxone. They found that rats treated with the combination of ceftriaxone and HU-211 suffered less cerebral edema and impairment of the BBB as compared to those treated with ceftriaxone alone.[2] These results are encouraging since, in spite of the recent advances in the medical sciences, bacterial and viral infections of the CNS still result in high mortality and morbidity.

Optic Nerve Damage

Yoles et al. have found that a single injection of HU-211 improved functional recovery of rat optic nerve subjected to a crush injury[26] (see Chapter 19).

Nerve Gas Damage

Exposure to the nerve gas soman is known to cause seizures and seizure-related brain damage. The initial effect of soman is the elevation of the levels of acetylcholine, a major neurotransmitter. One of the effects of acetylcholine is the release of large amounts of glutamic acid, which may lead to the development of excitotoxicity and cell death. NMDA antagonists, such as MK801, are known to reduce nerve gas cell death but due to their neurotoxic effects cannot be used in humans.

Filbert et al. have found that rats administered HU-211 (25 mg/kg, intraperitoneally) 5 to 40 min after exposure to a deadly dose of soman had above 80 percent reduction in brain lesion volume caused by the seizures, although HU-211 had no effect on the seizures.[9]

The conclusions of this important study were that "HU-211 provides considerable neuroprotection against brain damage produced by soman-induced seizures and suggests that it may be a valuable adjunct to current therapeutic regimens."[9]

Effects on the Dopaminergic System

Dopamine is a neurotransmitter, which, when chronically understimulated, may lead to Parkinson's disease. Striem et al. have demonstrated that HU-211 caused an elevation of dopamine levels and reduced the catalepsy produced by dopamine antagonists.[24] These observations may have therapeutic implications in Parkinson's disease.

The previous in vivo investigations are summarized in Table 36.2.

TABLE 36.2. Neuroprotective Effects of HU-211 in Vivo

Model	Effect	Reference
NMDA-induced tremor and convulsions (mice)	Increase of latency for effect	5
CHI (rat)	Improvement of motor and cognitive functions Reduction of edema and of BBB disruption	13,14
CHI (rat)	Inhibition of Ca accumulation in the brain	15
CHI (rat)	Inhibition of brain TNFα production	16
Pneumococcal meningitis (rats)	Reduction of edema and protection of BBB	21
Forebrain ischemia (gerbils)	Higher survival of CA1 hippocampal cells	17
Focal ischemia (rat)	Improvement of neurological outcome and reduction of infarct volume	18
Photochemical cortical infarction (rat)	Protection of BBB	20
Optic nerve crush	Improved response in visual evoked potential test	22
Dopamine effects	Enhanced dopamine activity	24
Soman (a nerve gas in rats)	Reduced brain lesions above 80%	23

Note: CHI = closed head injury; BBB = blood brain barrier; TNFα = tumor necrosis factor

DRUG DEVELOPMENT

The Israeli-American pharmaceutical company Pharmos, which has been involved in the development of HU-211 for the last six years, has completed a 14-day toxicological study in two species. Very low toxicity was found. In humans in Phase I clinical trials no side effects were observed up to a dose of 200 mg.[5]

In a phase II double-blind clinical trial (67 patients) in severe head trauma undertaken in six major hospitals in Israel, Knoller et al. found that elevations of intracranial pressure above a threshold of 20 or 25 mmHg were significantly attenuated in HU-211 treated patients, without concomitant reductions in systolic blood pressure.[11]

Reductions of cerebral perfusion pressure below a threshold to 50 mmHg were also significantly attenuated by the drug. Increase in intracranial or decrease in perfusion pressures are common complications after brain trauma and may cause severe damage or death. The incidence of hypotension was also significantly reduced in the drug-treated group.[11]

A consistent trend toward better overall outcome (favorable and good) as determined by a standard scale (Glasgow outcome scale) was observed in the severe patient subgroup.[11]

This very encouraging, clinical trial should make possible a wider Phase III clinical trial for head trauma.

SUMMARY

In vitro, HU-211 protects cells from overactivation of NMDA glutamate receptors from oxidative and free radical damage, and suppresses production of TNFα (a potentially highly toxic mediator).

In animals, HU-211 protects rats from the effects of closed head injury such as edema, blood brain barrier (BBB) disruption, motor and cognitive damage, calcium accumulation, and TNFα production. In pneumococcal meningitis it reduces edema and enhances BBB protection. In forebrain ischemia in gerbils it induces higher survival of hippocampal cells, and in focal cerebral ischemia in rats it reduces the infarct volume, lowers TNFα levels, and improves neurological outcome. HU-211 reduces very significantly the formation of brain lesions by the nerve gas soman.

In human patients, HU-211 administered up to 6 h after severe head trauma significantly reduced the elevation of intracranial pressure, and showed a consistent trend toward better outcome in the severe patient subgroup.

REFERENCES

1. Bar-Joseph A, Berkovitch Y, Adamchick J, Biegon A. Neuroprotective activity of HU-211, a novel NMDA antagonist, in global ischemia in gerbils. *Molecular and Chemical Neuropathology* 1994;23(2-3):125-135.

2. Bass R, Engelhard D, Trembovler V. Shohami E. A novel nonpsychotropic cannabinoid, HU-211, in the treatment of experimental pneumococcal meningitis. *Journal of Infectious Diseases* 1996;173(3):735-738.

3. Belayev L, Bar-Joseph A, Adamchik J, Biegon A. HU-211, a non-psychotropic cannabinoid, improves neurological signs and reduces brain damage, after severe forebrain ischemia in rats. *Molecular and Chemical Neuropathology* 1995; 25(1):19-33.

4. Belayev L, Busto R, Watson B, Ginsberg MD. Postischemic administration of HU-211, a novel noncompetitive NMDA antagonist, protects against blood-brain disruption in photochemical cortical infarction in rats: A quantitative study. *Brain Research* 1995;702(1-2):266-270.

5. Brewster ME, Pop E, Foltz RL, Reuschel S, Griffith W, Amselem S, Biegon A. Clinical pharmacokinetics of escalating i.v. doses of dexanabinol (HU-211), a neuroprotectant agent, in normal volunteers. *International Journal of Clinical Pharmacology and Therapeutics* 1997;35(9):361-365.

6. Eshhar N, Streim S, Biegon A. HU-211, a nonpsychotropic cannabinoid, rescues cortical neurons from excitatory amino acid toxicity in culture. *Neuroreport* 1993;5(3):237-240.

7. Eshhar N, Streim S, Kohen R, Tirosh O, Biegon A. Neuroprotective and antioxidant activities of HU-211, a novel NMDA receptor antagonist. *European Journal of Pharmacology* 1995;283(1-3):19-29.

8. Feigenbaum JJ, Bergmann F, Richmond SA, Mechoulam R, Nadler V, Kloog Y, Sokolovsky M. A nonpsychotropic cannabinoid acts as a functional *N*-methyl *D*-asparate (NMDA) receptor blocker. *Proceedings of the National Academy of Sciences of the United States of America* 1989;86(23):9584-9587.

9. Filbert MG, Forster JS, Smith CD, Ballough GP. Neuroprotective effects of HU-211 on brain damage resulting from soman-induced seizures. *Annals of the New York Academy of Sciences* 1999;890:505-514.

10. Gallily R, Yamin A, Waksman Y, Ovadia H, Weidenfeld J, Bar-Joseph A, Biegon A, Mechoulam R, Shohami E. Protection against septic shock and suppression of tumor necrosis factor α and nitric oxide production by dexanabinol (HU-211), a nonpsychotropic cannabinoid. *Journal of Pharmacology and Experimental Therapeutics* 1997;283(2):918-924.

11. Knoller N, Levi L, Israel Z, Razon N, Reichental E, Rappaport Z, Ehrenfreund N, Fiegon A. *Safety and outcome in a phase II clinical trial of dexanabinol in severe head trauma.* Presented at the Congress of Neurological Surgeons, 7 Oct. 1998, Seattle, Washington.

12. Leker RR, Shohami E, Abramsky O, Ovadia H. Dexanabinol: A novel neuroprotective drug in experimental focal cerebral ischemia. *Journal of the Neurological Sciences* 1999;162(2):114-119.

13. Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. *New England Journal of Medicine* 1994;330(9):613-622.

14. Little PJ, Compton DR, Mechoulam R, Martin B. Stereochemical effects of 11-OH-Δ^8-THC-dimethylheptyl in mice and dogs. *Pharmacology, Biochemistry and Behavior* 1989;32(3):661-666.

15. Mechoulam R, Devane WA, Glaser R. Cannabinoid geometry and biological activity. In Murphy L, Bartke A, eds. *Marijuana/cannabinoids: Neurobiology and neurophysiology*. Boca Raton, FL: CRC Press, 1992, pp. 1-33.

16. Mechoulam R, Feigenbaum JJ, Lander N, Segal M, Jarbe TUC, Hiltunen AJ, Consroe P. Enantiomeric cannabinoids: Stereospecificity of psychotropic activity. *Experientia* 1988;44:762-764.

17. Mechoulam R, Lander N, Breuer A, Zahalka J. Synthesis of the individual, pharmacologically distinct, enantiomers of a tetrahydrocannabinol derivative. *Tetrahedron: Asymmetry* 1990;1:315-319.

18. Nadler V, Biegon A, Beit-Yannai E, Adamchik J, Shohami J. [^{45}Ca] accumulation in rat brain after closed head injury; attenuation by the novel neuroprotective agent HU-211. *Brain Research* 1995;685(A-2):1-11.

19. Nadler V, Mechoulam R, Sokolovsky M. Blockage of $^{45}Ca^{2+}$ influx through the *N*-methyl *D*-aspartate receptor ion channel by the nonpsychoactive cannabinoid HU-211. *Brain Research* 1993;622(1-2):79-85.

20. Nadler V, Mechoulam R, Sokolovsky M. The nonpsychotropic cannabinoid (+)-(3S,4S)-7-hydroxy-delta-6-tetrahydrocannabinol 1,1-dimethylheptyl (HU-211) attenuates *N*-methyl *D*-aspartate-receptor-mediated neurotoxicity in primary cultures of rat forebrain. *Neuroscience Letters* 1993;162(1-2):43-45.

21. Shohami E, Bass R, Ben Hur T, Gallily R. Cytokine production in the brain following closed head injury: TNF-α inhibition is associated with cerebroprotection. *European Cytokine Network* 1996;7:309.

22. Shohami E, Novikov M, Bass R. Long-term effect of HU-211, a novel noncompetitive NMDA antagonist, on motor and memory functions after closed head injury in the rat. *Brain Research* 1995;674(1):55-62.

23. Shohami E, Novikov M, Mechoulam R. A nonpsychotropic cannabinoid, HU-211, has cerebroprotective effects after closed head injury. *Journal of Neurotrauma* 1993;10(2):109-119.

24. Striem S, Bar-Joseph A, Berkovitch Y, Biegon A. Interaction of dexanabinol (HU-211), a novel NMDA receptor antogonist, with the dopaminergic system. *European Journal of Pharmacology* 1997;338(3):205-213.

25. Tracey KJ, Cerami A. Tumor necrosis factor: A pleiotropic cytokine and therapeutic target. *Annual Review of Medicine* 1994;45:491-503.

26. Yoles E, Belkin M, Schwartz M. HU-211, a nonpsychotropic cannabinoid, produces short- and long-term neuroprotection after optic nerve axotomy. *Journal of Neurotrauma* 1995;13(1):49-57.

PART VI: OTHER CONSTITUENTS OF CANNABIS

Chapter 37

Noncannabinoid Components

John M. McPartland
Vito Mediavilla

INTRODUCTION

Cannabis is a veritable chemical factory, producing hundreds of compounds.[35] Mechoulam et al.[20] suggested that the noncannabinoid constituents in herbal cannabis may work by multiple mechanisms to influence THC activity. Carlini et al.[7] determined that cannabis extracts produced effects "two or four times greater than that expected from their THC content," based on animal and human studies. Similarly, Fairbairn and Pickens[10] detected the presence of unidentified "powerful synergists" in cannabis extracts, causing 330 percent greater cataleptic activity in mice than THC alone.

In addition to therapeutic synergism, a second benefit of herbal medicines is a *reduced side effect profile;* herbalists claim that polypharmaceutical herbs contain compounds that mitigate the side effects of their primary active ingredients.[19] Indeed, pure THC elicits a higher incidence of "overdose" reactions than does herbal cannabis, seen as symptoms of dysphoria, depersonalization, anxiety, panic reactions, and paranoia.[15]

The cannabis constituents that enhance beneficial THC activity and reduce THC side effects, however, are seldom identified or discussed. Zuardi, elsewhere in this volume, addresses CBD (see Chapter 33). This review will focus on two classes of constituents: terpenoids and flavonoids.

TERPENOIDS

The unique smell of cannabis comes not from cannabinoids, but from volatile terpenoids (see Chapter 3). Terpenoids are polymers composed of repeating units of isoprene (C_5H_8)—the monoterpenoids (with C_{10} skele-

tons), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), and triterpenoids (C_{30}). Terpenoids may be acyclic, monocyclic, or polycyclic hydrocarbons; they may have alcohol, ether, aldehyde, ketone, or ester functional groups.

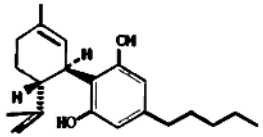
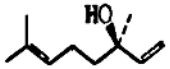
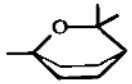
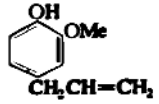
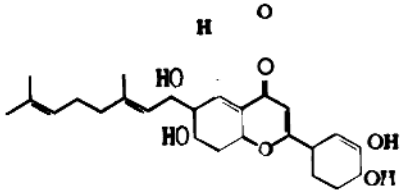
Cannabis produces over 100 terpenoids.[21,30,35] (See Table 37.1 for a few examples.) Collectively, terpenoids are called the *essential oil* or volatile oil of the plant. Field-cultivated cannabis yields about 1.3 liters of essential oil per ton fresh weight plants.[21] Industrial extraction of essential oil is done using steam distillation. The yield of essential oil increases when pollination is prevented (18 l/ha in sinsemilla crops, versus 8 l/ha in pollinated crops).[22] The composition and concentration of terpenoids varies between strains of cannabis[21] and harvest dates.[22] Many terpenoids vaporize at relatively low temperatures (see Table 37.1), especially compared to THC, which boils at 157°C. Thus, terpenoids can be quite ephemeral; the drying and storing of cannabis causes significant losses, and monoterpenoids are lost faster than sesquiterpenoids.[30]

Terpenoids are lipophilic and permeate membranes. Many cross the blood-brain barrier (BBB) after inhalation.[4,26] Inhaled terpenoids may modulate THC activity by several mechanisms: (1) Some terpenoids dock at cannabinoid receptors. Thujone, a terpenoid from *Artemisia absinthium,* has a slight affinity for CB_1 receptors, with a Ki = 130 μM.[23] Terpenoids shared by *Artemisia* and *Cannabis,* such as borneol acetate, fenchone, *p*-cymene, and limonene, may also bind to CB_1 receptors.[23] (2) Terpenoids may modulate the affinity of THC for its own receptor—by sequestering THC, by perturbing annular lipids surrounding the receptor, or by increasing the fluidity of neuronal membrane.[23] (3) Terpenoids may remodel G-proteins via nonreceptor mechanisms;[14] G-proteins carry intracellular signals downstream from CB receptors. (4) Terpenoids may alter the pharmacokinetics of THC by changing the BBB; cannabis extracts cause a significant increase in BBB permeability.[1] Indirectly, terpenoids modulate THC activity by acting on other receptors and neurotransmitters. Some terpenoids act as serotonin uptake inhibitors, enhance norepinephrine activity, increase dopamine activity, and augment gamma-aminobutyric acid (GABA).[19]

Generally, inhaled terpenoids cause sedation. Buchbauer et al.[4] assayed the sedative effects of over 40 terpenoids on mice; many highly sedating terpenoids are found in cannabis, including linalool, citronellol, and α-terpineol. Sedation may mitigate the anxiety occasionally provoked by administration of THC.[19] Similarly, cannabidiol (CBD) sedates anxiety precipitated by pure THC (see Chapter 33).

Terpenoids may mitigate memory loss. THC decreases acetylcholine in the hippocampus,[8] creating a deficit similar to that seen in patients with Alzheimer's disease. Alzheimer's patients are treated with acetylcholinesterase inhibitors, such as tacrine. Cannabis terpenoids also act as acetylcholinesterase

TABLE 37.1. Six Representative Constituents of Cannabis with Their Relational Structures, Concentrations, and Activities

Constituent (class of compound)	Chemical structure	Yield (w/w) in dried Cannabis	Boiling temperature	Physiological activity
cannabidiol CBD (cannabinoid)		0.5-1.5%	160-180°C	Reverse agonist of THC receptor Inhibits hydroxylation of THC to 11-OH-THC Sedative, anxiolytic, antipsychotic Enhances activity of brain amines
linalool (terpenoid)		0.002%	198°C	Sedative, anxiolytic
limonene (terpenoid)		0.14%	176°C	Increases cerebral acetylcholine activity (decreases memory loss) Antibacterial, antifungal
1,8-cineole (terpenoid)		>0.01%	176°C	Increases cerebral acetylcholine activity Increases cerebral blood flow Enhances cortical activity
eugenol (phenol)		>0.01%	121°C	Anti-inflammatory, antibacterial
cannflavin A (flavonoid)		0.019%	M.P. 182°C	Anti-inflammatory May enhance immune function

(AchE) inhibitors, including limonene, limonene oxide, α-terpinene, γ-terpinene, terpinen-4-ol, carvacrol, *l*- and *d*-carvone, 1,8-cineole, *p*-cymene, fenchone, pulegone, and pulegone-1,2-epoxide (reviewed elsewhere[19]).

Brain function is enhanced by administering terpenoids that improve cerebral blood flow, such as the ginkgolides in *Ginkgo biloba*. Studies show the inhalation of 1,8-cineole, a monoterpenoid in cannabis, increases cerebral blood flow and enhances cortical activity.[26] Similarly, cerebral blood flow increases after inhaling marijuana smoke, and the increase is *not* related to plasma levels of THC.[18]

Terpenoids may mitigate side effects caused by burning and inhaling marijuana. Limonene, for instance, blocks the carcinogenesis induced by benz[α]anthracene.[14] Many terpenoids exhibit antimicrobial activity, which may explain why terpenoid-rich marijuana is relatively free of contamination by pathogenic bacteria and fungi. This is an important consideration for immunocompromised individuals. For a review of microbes isolated from marijuana, see Chapter 30; antimicrobial terpenoids are reviewed elsewhere.[19]

Anti-inflammatory terpenoids may explain why the inhalation of aerosolized THC causes more airway irritation than marijuana smoke.[34] Carvacrol in cannabis smoke potently inhibits prostaglandin production, more so than THC or CBG.[6] Beta-caryophyllene exhibits little anti-inflammatory activity by itself, but its activity is compounded by other terpenoids, such as α-pinene.[19] Indeed, unfractionated cannabis oil exhibits greater anti-inflammatory activity than its individual constituents, suggesting synergy.[9]

FLAVONOIDS

Flavonoids are aromatic, polycyclic phenols (see Chapter 3). About 20 are found in cannabis, as free flavonoids and conjugated glycosides.[35] Apigenin, kaempferol, luteolin, orientin, and quercetin exist in many plants; other flavonoids are unique to cannabis, such as the cannflavins.[2] Flavonoids, like terpenoids, exert a wide range of biological effects. Some are lipophilic, permeate membranes, and cross the BBB. Flavonoids are volatile, can be collected by steam distillation, and apparently retain pharmacological activity in marijuana smoke.[5,32]

Flavonoids in cannabis inhibit prostaglandin E_2 production, more than cannabinoids *and* terpenoids.[9] Anti-inflammatory activity is also exhibited by flavonoid-related phenols in cannabis (e.g., eugenol),[6] and marijuana smoke (e.g., *p*-vinylphenol).[5] Apigenin inhibits tumor necrosis factor (TNF)-induced inflammation.[12]

Quercetin and other flavonoids are potent antioxidants; some flavonoids show greater activity than ascorbic acid, α-tocopherol, and butylated

hydroxytoluene (BHT).[36] Flavonoids break the chain of free radical formation at several steps—by scavenging superoxide anions (in enzymic and nonenzymic systems), by quenching intermediate peroxyl and alkoxyl radicals, and by chelating iron ions, which catalyze many Fenton reactions leading to free radical formation.[25] The oxidation potentials of flavonoids should be tested against cannabidiol (CBD); perhaps flavonoids can reduce CBD, allowing it to recycle as an antioxidant. (For antioxidant activity of CBD, see Chapter 9.)

The pharmacokinetics of THC may be modulated by flavonoids, via many mechanisms described in the terpenoid section. Flavonoids are particularly adept at inhibiting cytochrome P450 (CYP) monoxygenase enzymes. CYPs catalyze the metabolism of THC to 11-hydroxy-THC (see Chapter 6). More 11-OH-THC appears in the bloodstream when THC is orally administered than when THC is inhaled, due to a preponderance of CYPs in the small intestine and liver (the "first-pass metabolism" of orally-administered drugs). The 11-hydroxy metabolite is four times more psychoactive than unmetabolized THC,[19] and four times more immunosuppressive.[17] CBD inactivates CYPs belonging to the 2C and 3A subfamilies, but CBD's effects are complex—it decreases the metabolism of THC to 11-OH-THC in vitro, yet it markedly increases 11-OH-THC levels in mouse brains.[3] CBD also increases the serum levels of other drugs metabolized by CYP 3A enzymes, such as cyclosporine.[16] Administration of naringenin, a flavonoid in grapefruit juice, similarly inhibits CYP 3A4 and augments levels of cyclosporine, caffeine, benzodiazepines, and calcium antagonists.[11]

Some CYP enzymes metabolize environmental toxins, from procarcinogens to their activated forms, especially CYP 1A1 and CYP 3A4. Thus, CYP-suppressing flavonoids serve as chemoprotective agents, shielding healthy cells from procarcinogens such as benzo[α]pyrene and aflatoxin B_1,[27] two harmful agents potentially found in marijuana smoke (see Chapter 30).

CYP suppression by some flavonoids increases acetylcholinesterase activity,[29] potentially improving memory by synergizing the effects of terpenoids, as described previously. Indeed, by some parameters, apigenin improved memory behavior in rodents.[31] In the same study, apigenin provided anxiolytic effects, without evidencing sedative actions, by acting as a central benzodiazepine receptor agonist.[31]

Last, apigenin and other flavonoids interact with estrogen receptors, and appear to be the primary estrogenic agents in marijuana smoke.[32] Although apigenin has a high affinity for estrogen receptors (especially β-estrogen receptors), it has low estrogenic activity; apigenin actually inhibits estradiol-induced proliferation of breast cancer cells.[37]

CONCLUSIONS

Do noncannabinoids exist in physiologically relevant concentrations? In the absence of experimental data, we can estimate, using limonene as an example. According to Ross and ElSohly,[30] the concentration of essential oil in buds of air-dried cannabis is 0.8 percent. Limonene consists of 17.20 percent of the essential oil, equaling 0.14 percent of air-dried cannabis.[30] Thus, a 900 mg joint contains 1.26 mg limonene. If we assume the systemic bioavailability of limonene from smoking a joint is 18 percent, the same as THC,[28] then 0.23 mg would be absorbed. If this dose was evenly distributed in the total body water of a 70 kg man, without metabolism or sequestration, then the maximum tissue concentration of limonene from a single joint would be approximately 2.3 μM. This concentration is an order of magnitude below the IC_{50} concentration of limonene's inhibition of AchE, according to Miyazawa et al.[24] We conclude that limonene would have to synergize with other AchE inhibitors to be effective.

Polypharmaceutical cannabis has been characterized as a "synergistic shotgun," in contrast with single-ingredient "silver bullets," such as THC (dronabinol).[19] The paucity of research concerning non-THC synergists in marijuana is periodically criticized.[19,20,33] Here we highlight several terpenoid and flavonoid constituents that deserve attention. Other non-THC compounds with proven pharmacological activity include poorly characterized glycoproteins, alkaloids, phytosterols, and compounds that remain completely unidentified.[13]

REFERENCES

1. Agrawal AK, Kumar P, Gulati A, Seth PK. Cannabis-induced neurotoxicity in mice: Effects on cholinergic (muscarinic) receptors and blood-brain barrier permeability. *Research Communications in Substance Abuse* 1989;10:155-168.

2. Barrett ML, Scutt AM, Evans FJ. Cannflavin A and B, prenylated flavones from *Cannabis sativa* L. *Experientia* 1986;42(4):452-453.

3. Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metabolism and Disposition* 1995;23(8):825-831.

4. Buchbauer G, Jirovetz L, Jäger W, Plank C, Dietrich H. Fragrance compounds and essential oils with sedative effects upon inhalation. *Journal of Pharmaceutical Sciences* 1993;82(6):660-664.

5. Burstein S, Taylor P, El-Feraly FS, Turner C. Prostaglandins and cannabis—V. Identification of p-vinylphenol as a potent inhibitor of prostaglandin synthesis. *Biochemical Pharmacology* 1976;25(17):2003-2004.

6. Burstein S, Varanelli C, Slade LT. Prostaglandins and cannabis—III. Inhibition of biosynthesis by essential oil components of marihuana. *Biochemical Pharmacology* 1975;24(9):1053-1054.

7. Carlini EA, Karniol IG, Renault PF, Schuster CR. Effects of marihuana in laboratory animals and man. *British Journal of Pharmacology* 1974;50(2):299-309.

8. Carta G, Nava F, Gessa GL. Inhibition of hippocampal acetylcholine release after acute and repeated Δ^9-tetrahydrocannabinol in rats. *Brain Research* 1998; 809(1):1-4.

9. Evans AT, Formukong EA, Evans FJ. Actions of cannabis constituents on enyzmes of arachidonate metabolism: Anti-inflammatory potential. *Biochemical Pharmacology* 1987;36(12):2035-2037.

10. Fairbairn JW, Pickens JT. Activity of cannabis in relation to its delta'-*trans*-tetrahydrocannabinol content. *British Journal of Pharmacology* 1981;72(3):401-409.

11. Fuhr U. Drug interactions with grapefruit juice. Extent, probable mechanism and clinical relevance. *Drug Safety* 1998;18(4):251-272.

12. Gerritsen ME, Carley WW, Ranges GE, Shen C-P, Phan SA, Ligon GF, Perry CA. Flavonoids inhibit cytokine-induced endothelial cell adhesion protein gene expression. *American Journal of Pathology* 1995;147(2):278-292.

13. Gill EW, Paton WDM, Pertwee RG. Preliminary experiments on the chemistry and pharmacology of cannabis. *Nature* 1970;228(267):134-136.

14. Gould MN. Cancer chemoprevention and therapy by monoterpenes. *Environmental Health Perspectives* 1997;105(Suppl. 4):977-979.

15. Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine*, revised edition. New Haven, CT: Yale University Press, 1997.

16. Jaeger W, Benet LZ, Bornheim LM. Inhibition of cyclosporine and tetrahydrocannabinol metabolism by cannabidiol in mouse and human microsomes. *Xenobiotica* 1996;26(3):275-284.

17. Klein TW, Newton C, Friedman H. Inhibition of natural killer cell function by marijuana components. *Journal of Toxicology and Environmental Health* 1987; 20(4):321-232.

18. Mathew RJ, Wilson WH. Acute changes in cerebral blood flow after smoking marijuana. *Life Sciences* 1993;52(8):757-767.

19. McPartland JM, Pruitt PL. Side effects of pharmaceuticals not elicited by comparable herbal medicines: The case of tetrahydrocannabinol and marijuana. *Alternative Therapies in Health and Medicine* 1999;5(4):57-62.

20. Mechoulam R, Ben-Zvi Z, Shani A, Zemler H, Levy S. Cannabinoids and cannabis activity. In *Cannabis and its derivatives*. Paton WDM, Crown J, eds. London: Oxford University Press, 1972, pp. 1-13.

21. Mediavilla V, Steinemann S. Essential oil of *Cannabis sativa* L. strains. *Journal of the International Hemp Association* 1997;4(2):82-84.

22. Meier C, Mediavilla V. Factors influencing the yield and the quality of hemp (*Cannabis sativa* L.) essential oil. *Journal of the International Hemp Association* 1998;5(1):16-20.

23. Meschler JP, Howlett AC. Thujone exhibits low affinity for cannabinoid receptors but fails to evoke cannabimimetic responses. *Pharmacology, Biochemistry and Behavior* 1999;62(3):473-480.

24. Miyazawa M, Watanabe H, Kameoka H. Inhibition of acetylcholinesterase activity by monoterpenoids with a *p*-methane skeleton. *Journal of Agricultural Food Chemistry* 1997;45:677-9.

25. Musonda CA, Chipman JK. Quercetin inhibits hydrogen peroxide (H_2O_2)-induced NF-κB DNA binding activity and DNA damage in HepG2 cells. *Carcinogenesis* 1998;19(9):1583-1589.

26. Nasel C, Nasel B, Samec P, Schindler E, Buchbauer G. Functional imaging of effects of fragrances on the human brain after prolonged inhalation. *Chemical Senses* 1994;19(4):359-364.

27. Offord EA, Macé K, Avanti O, Pfeifer AMA. Mechanisms involved in the chemoprotective effects of rosemary extract studied in human liver and bronchial cells. *Cancer Letters* 1997;114(1-2):275-281.

28. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma Δ^9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 1980;28(3):409-416.

29. Ramos S, Sultatos L. Flavonoid-induced alterations in cytochrome P450-dependent biotransformation of the organophosphorus insecticide parathion in the mouse. *Toxicology* 1998;131(2-3):155-167.

30. Ross SA, ElSohly MA. The volatile oil composition of fresh and air-dried buds of *Cannabis sativa*. *Journal of Natural Products* 1996;59(1):49-51.

31. Salgueiro JB, Ardenghi P, Dias M, Ferreira MBC, Izquierdo I, Medina JH. Anxiolytic natural and synthetic flavonoid ligands of the central benzodiazepine receptor have no effect on memory tasks in rats. *Pharmacology, Biochemistry and Behavior* 1997;58(4):887-891.

32. Sauer MA, Rifka SM, Hawks RL, Cutler GB, Loriaux DL. Marijuana: Interaction with the estrogen receptor. *Journal of Pharmacology and Experimental Therapeutics* 1983;224(2):404-407.

33. Schurr A. Marihuana: Much ado about THC. *Comparative Biochemistry and Physiology* 1985;80(1):1-7.

34. Tashkin DP, Reiss S, Shapiro BJ, Calvarese B, Olsen JL, Lodge JW. Bronchial effects of aerosolized Δ^9-tetrahydrocannabinol in healthy and asthmatic subjects. *American Review of Respiratory Disease* 1977;115(1):57-65.

35. Turner CE, Elsohly MA, Boeren EG. Constituents of *Cannabis sativa* L. XVII. A review of the natural constituents. *Journal of Natural Products* 1980; 43(2):169-304.

36. Vinson JA. 1998. Flavonoids in foods as in vitro and in vivo antioxidants. In Manthey JA, Busling BG, eds. *Flavonoids in the living system.* NY: Plenum Press, 1998.

37. Wang C, Kurzer MS. Effects of phytoestrogens on DNA synthesis in MCF-7 cells in the presence of estradiol or growth factors. *Nutrition and Cancer* 1998;31(2):90-100.

Chapter 38

Hemp Seed and Hemp Oil

Gero Leson
Petra Pless

INTRODUCTION

Until recently, most of the discussion about the potential therapeutic benefits from *Cannabis sativa* has focused on cannabinoids. Largely unknown, yet increasingly popular, are other cannabis products which provide nutritional and possibly therapeutic benefits, i.e., hemp seeds and hemp oil—the oil pressed from hemp seeds. Historical accounts name hemp seeds as a cure for numerous diseases: as an analgesic; for sores and skin diseases; and for coughs, jaundice, and colic. However, these accounts did often not distinguish between effects from the seeds and the cannabinoids contained in the flowers, respectively. Hemp seeds, the by-product of hemp grown for fiber, were primarily used for food. Their oil also was processed into paints, varnishes, and soap. Along with the demise of hemp fiber during the last century, hemp seeds also lost their significance.

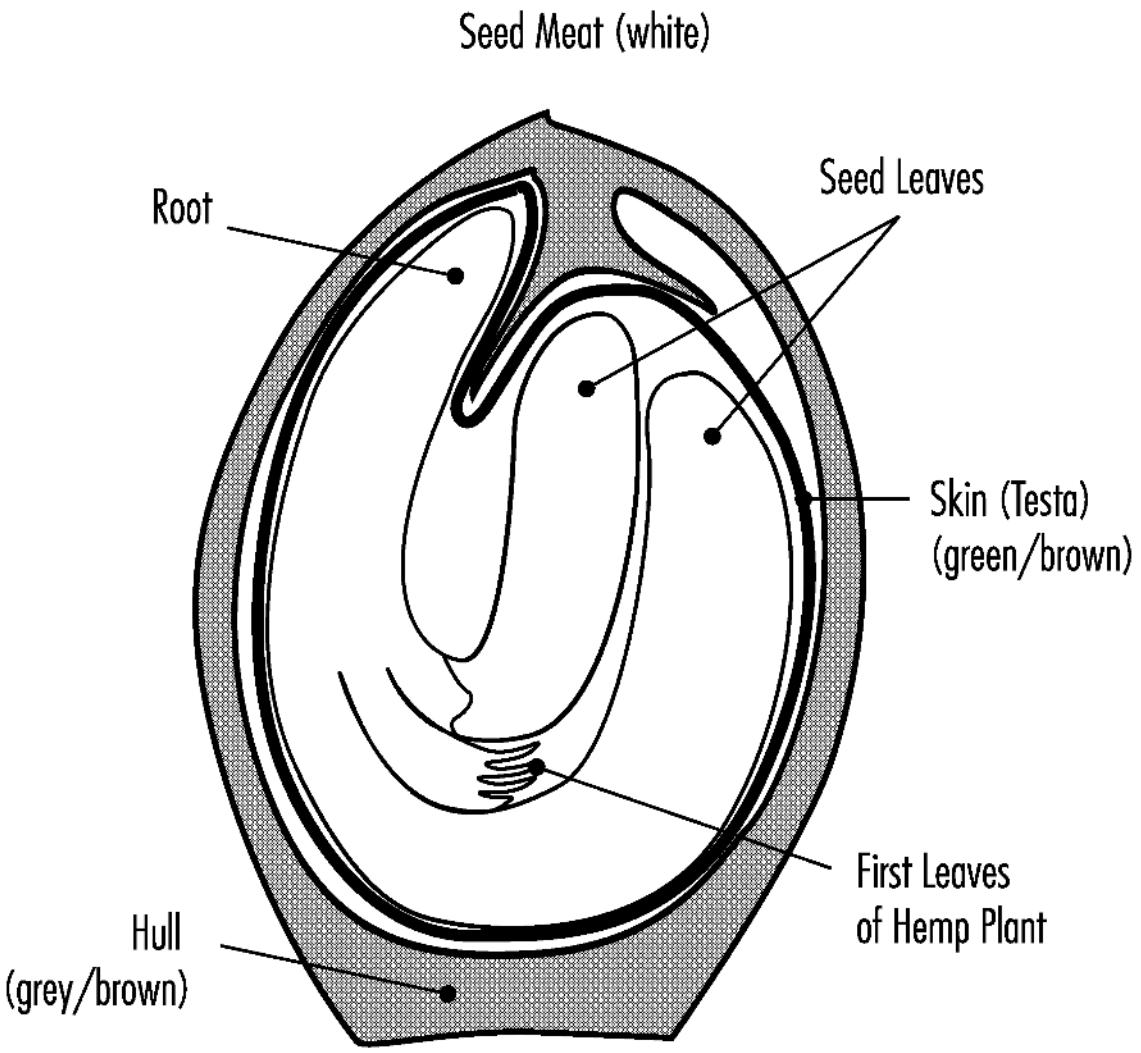
During the last three decades, world hemp seed production fell from 100,000 metric tons/year to about 40,000 tons/year. Hemp seeds are primarily used and traded internationally for birdseed. In countries such as China, the largest producer of hemp seeds in the world, the toasted whole seeds are also used as snacks.

Modern medical and nutritional research and the expanding knowledge of the composition of hemp seeds now suggest that particularly its fatty acid spectrum renders hemp oil a balanced and tasty source of essential and other rare fatty acids for human consumption. Hemp seeds, which are now offered as hulled seeds or "hemp nuts" in Europe and the United States, also supply essential amino acids, vitamin E, and other relevant nutrients. The composition of hemp seeds and oil and their potential nutritional and therapeutic benefits are briefly discussed in the following section. More extensive over-

views and references to specific scientific publications on technical and health aspects of fatty acids are provided in the literature.[2,3,5,10,13,16,21]

Botanically, hemp seeds are small nuts, typically a few millimeters in diameter. They are somewhat shorter and thicker than sunflower seeds. Figure 38.1 shows a vertical cut through a hemp seed. A thin, crunchy, edible hull protects their meat. This meat, which can be extracted from the seeds by careful hulling, typically contains about 45 percent fat and 35 percent protein. Sugars, ash, and moisture account for most of the remainder. Table 38.1 lists the typical composition of whole and hulled seeds; Figure 38.2 displays the results.

FIGURE 38.1. Vertical Cut Through a Hemp Seed



Source: Leson G, Pless P, Roulac J. *Hemp Foods and Oils for Health.* Sebastopol, CA: Hemptech, 1999.

TABLE 38.1. Typical Specifications for Whole and Hulled Hemp Seeds and Hemp Seed Flower

Nutritional Analyses	Whole Hemp seeds	Hulled Hemp seeds	Hemp seed Flour
Energy	500 kCal/100 g	580 kCal/100 g	
Protein	23 g/100 g	33 g/100 g	31 g/100 g
Total fat	31 g/100 g	44 g/100 g	8 g/100 g
Saturated	3 g/100 g	5 g/100 g	
Unsaturated	28 g/100 g	39 g/100 g	
Carbohydrates	34 g/100 g	12 g/100 g	45 g/100 g
Dietary fiber	33 g/100 g	7 g/100 g	
Sugars	1 g/100 g	3 g/100 g	
Ash	6 g/100 g	6 g/100 g	8 g/100 g
Moisture	6 g/100 g	5 g/100 g	8 g/100 g
Minerals			
Calcium	70-180 mg/100 g	10-20 mg/100 g	180-250 mg/100 g
Iron	5-20 mg/100 g	2-5 mg/100 g	20-30 mg/100 g
Sodium	2-10 mg/100 g	1-2 mg/100 g	10-20 mg/100 g
THC content	5-30 ppm	<2 ppm	5-30 ppm

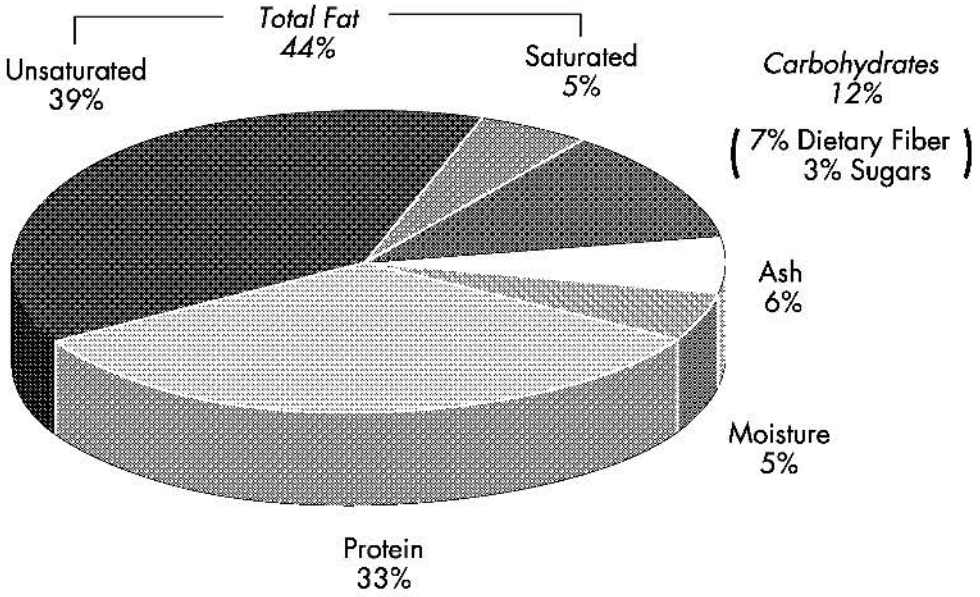
Source: Leson G, Pless P, Roulac J. *Hemp Foods and Oils for Health.* Sebastopol, CA: Hemptech, 1999.

COMPOSITION OF HEMP OIL

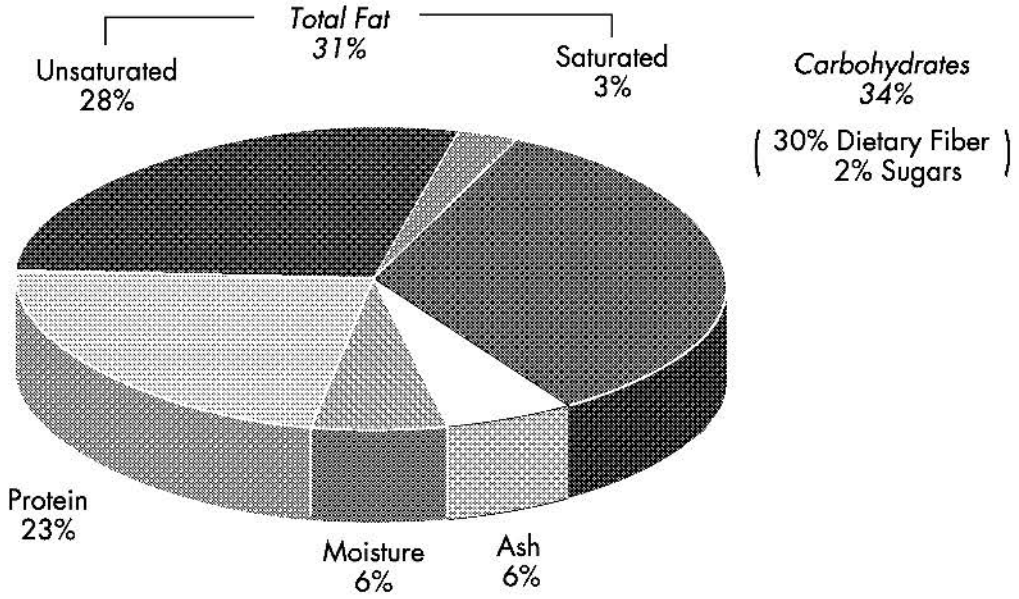
Much of the recent interest in hemp seeds has focused on the use of their oil for food and body care applications. Consequently, most of the analytical data available for hemp seed products are for the fatty acid (FA) spectrum of hemp oil. Although this spectrum depends considerably on hemp variety, or

FIGURE 38.2. Composition of Whole and Hulled Hemp Seeds

Hulled Hemp seed

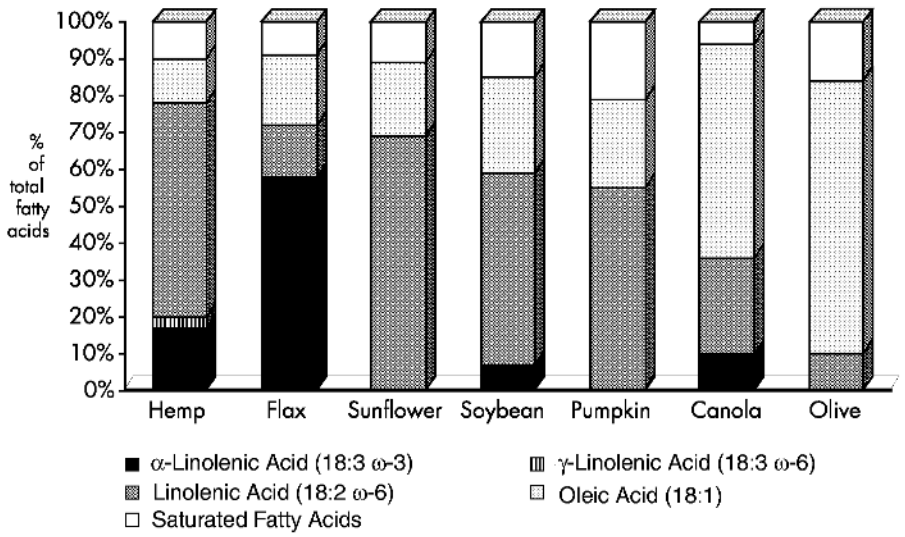


Whole Hemp seed



Source: Leson G, Pless P, Roulac J. *Hemp Foods and Oils for Health.* Sebastopol, CA: Hemptech, 1999.

FIGURE 38.3. Typical Fatty Acid Composition of Unrefined Vegetable Oils



Source: Leson G, Pless P, Roulac J. *Hemp Foods and Oils for Health.* Sebastopol, CA: Hemptech, 1999.

cultivar, several general characteristics of hemp oil may be noted. Table 38.2 lists typical specifications for unrefined hemp oil. Figure 38.3 compares its FA spectrum with that of other common food oils. These data suggest the following:

1. The essential fatty acids (EFAs), linoleic acid (LA, 18:2 omega-6) and α-linolenic acid (ALA, 18:3, omega-3) typically account for 75 percent of FAs. (Chemical nomenclature of fatty acids: a fatty acid with the formula "*x:y* omega-z" is *x* carbon atoms long, has *y* double-bonds, with the first double-bond on the *z*th carbon atom, counted from the omega, or methyl end. See Figure 38.4). LA and ALA are also referred to as parent compounds of the ω-3 and ω-6 families, respectively. These families are shown in Figure 38.5. EFAs cannot be synthesized in humans and must be present in the diet. The triple-unsaturated ALA accounts for a significant fraction thereof, typically 15-25 percent of total FAs. Oleic acid and total saturated FAs each contribute about 10 percent.
2. Hemp oil contains several "higher FAs," i.e., those which the human body metabolizes from the two EFAs, respectively. Most notable are γ-linolenic acid (GLA, 18:3 ω-6) and stearidonic acid (SDA, 18:4 ω-3),

i.e., the first metabolites in the ω-6 and ω-3 families, respectively. The content of such higher FAs varies considerably with variety and growing conditions. Generally, varieties adapted to northern latitudes produce oils with higher GLA and SDA concentrations. (FIN-314, a cultivar bred in Finland and now grown in Canada, has GLA and SDA levels of 4 percent and 2 percent, respectively.)

3. These characteristics of hemp oil have several nutritional and health implications:

   - Most commonly used oils (sunflower, soy, canola, and corn) provide sufficient LA. However, only soybean and canola oils also provide a small amount of the w-3 ALA. Flax, which is rich in ALA, is not suitable for cooking due to this FA's oxidative instability and the oil's taste. Since meat and grain are also not relevant sources of ALA or higher w-3 FAs, the diet of people in Western countries is routinely deficient in w-3s. There is growing evidence that omega-3 deficiency contributes to several common acute and chronic illnesses. The typical ratio of LA to ALA in hemp oil is close to the 4:1 to 6:1 ratio considered optimal by nutritionists.[19] This ratio is considerably lower than in all vegetable oils commonly used for cooking, except for canola (rapeseed).
   - The presence of smaller proportions of GLA and SDA offers additional benefits to those in whom the metabolic conversion of the two EFAs to higher FAs is inhibited by genetic, dietary, or other lifestyle factors, thus, contributing to various diseases.
   - Finally, hemp oil contains moderate to high concentrations of antioxidants of the vitamin E complex (100 to 150 mg per 100 grams of oil, primarily g-tocopherol) and modest amounts of several other beneficial or even essential constituents (phytosterols, phospholipids, carotenes, and several minerals).

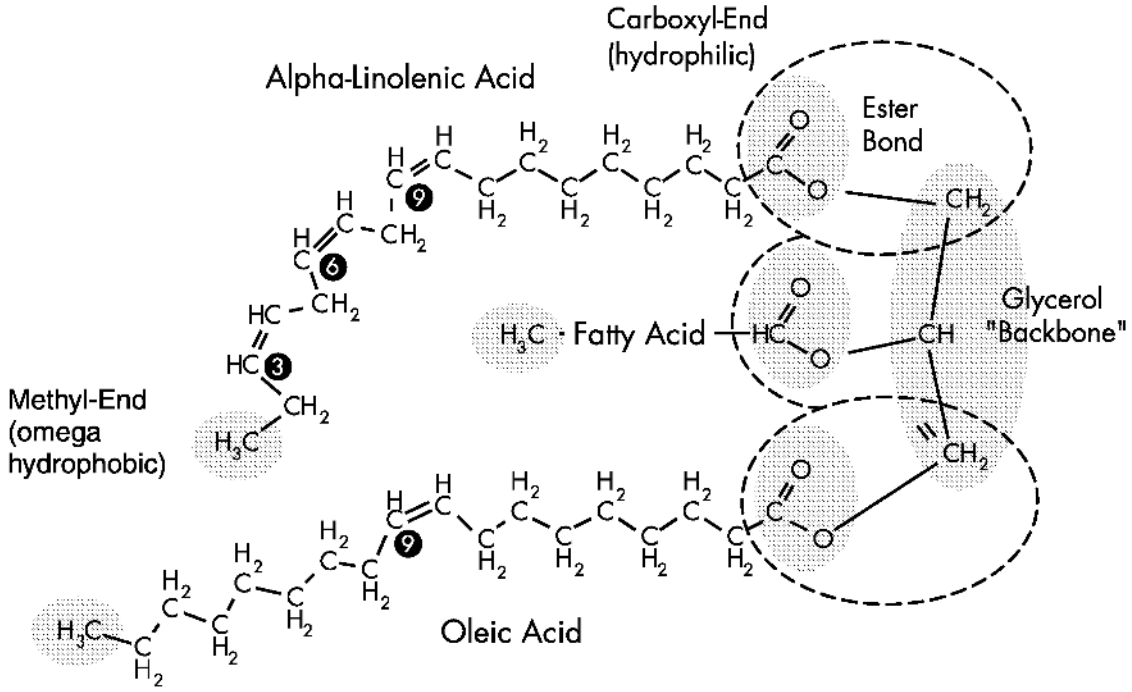
The composition of hemp oil in comparison with other oils shows that it is not exceptionally high in any of the fatty acids or other constituents that are crucial to human health and are nowadays often consumed as nutritional supplements. For example, flax and evening primrose oil contain higher concentrations of ALA and GLA, respectively (see Figure 38.5). Yet, their instability, unpleasant taste, or higher cost render these oils unsuitable as food oils. Hemp seeds, on the other hand, if carefully handled and cold-pressed, yield a tasty oil. With the exception of frying and deep-frying, hemp seed oil may be used in the preparation of salads, dips, sauces, soups, and for sautéing. Thus, the value of hemp oil lies in the combination of its desirable fatty acid spectrum with its nutritional versatility and a flavor at-

TABLE 38.2. Typical Specifications for Unrefined Hemp Oil

Analyses	Hemp Oil
Fatty Acid	
Saturated fatty acids	in % of total fatty acids
Palmitic acid (16:0)	6-9%
Stearic acid (18:0)	2-3.5%
Arachidic acid (20:0)	1-3%
Behenic acid (22:0)	<0.3%
Total saturated fatty acid	9-11%
Unsaturated fatty acids	in % of total fatty acids
Oleic acid (18:1 ω-9)	8.5-16%
Linoleic acid (18:2 ω-6)	53-60%
γ-Linolenic acid GLA (18:3 ω-6)	1-4%
α-Linolenic acid (18:3 ω-3)	15-25%
Stearidonic acid (18:4 ω-3)	0.4-2%
Eicosanoic acid (20:1)	<0.5%
Total unsaturated fatty acids	89-91%
Chemical Analyses	
Vitamin E	100-150 mg/100 g (mostly γ-tocopherol) 13-20 IU/100g (as α-tocopherol equivalents)
Chlorophyll	50-20 ppm
THC content	2-20 ppm
Specific gravity	0.92 kg/l
Iodine value	155-170
Peroxide value	4-7 meq O2/kg
Free fatty acids	1.5-2.0% as Oleic Acid
Phosphatides	100-400 ppm
Smoke point	330°F (165°C)
Melting point	18°F (–8°C)

Source: Leson G, Pless P, Roulac J. *Hemp Foods and Oils for Health.* Sebastopol, CA: Hemptech, 1999.

FIGURE 38.4. Chemical Structure of α-Linolenic and Oleic Acids in a Triglyceride



Source: Leson G, Pless P, Roulac J. *Hemp Foods and Oils for Health.* Sebastopol, CA: Hemptech, 1999.

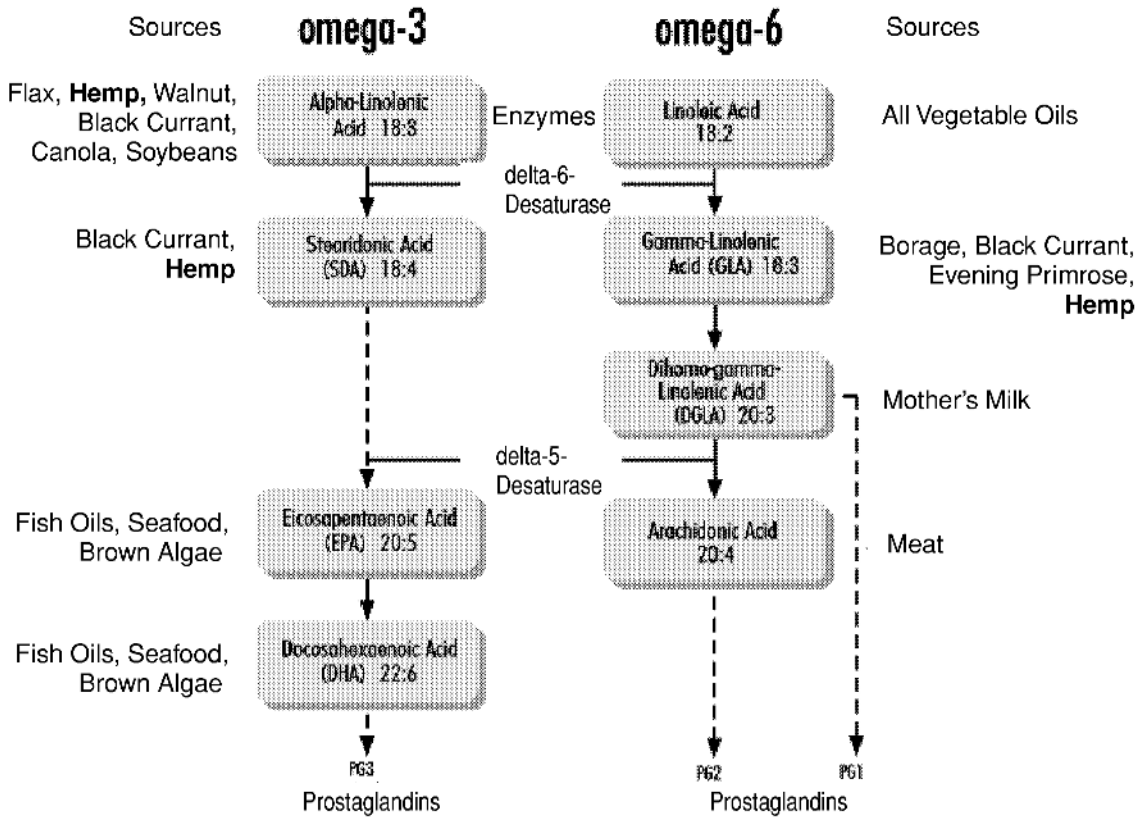
tractive to many, rendering it a promising ingredient of modern "functional foods."

NUTRITIONAL AND THERAPEUTIC BENEFITS OF HEMP OIL

Over the last three decades, extensive research has been conducted on the role of fatty acid supply in the development of many common diseases. Much of this work has focused on the impact of fat intake on the genesis of cardiovascular diseases. It suggests that excessive consumption of saturated fatty acids via meat and fried foods raises blood levels of LDL (low density lipoprotein) cholesterol and contributes to the formation of arterial plaque, thus raising the risk of heart attacks and strokes.

More recently, numerous studies have also evaluated the impact of FA intake on the occurrence of some of the more common diseases in Western countries. In summary, the findings indicate that an imbalance in ω-3 and ω-6 fatty acids intake and, consequently, an imbalance in the formation of their metabolites, the prostaglandins, is often a cofactor in the development of these diseases. Figure 38.5 shows a schematic of the metabolic pathways of

FIGURE 38.5. Metabolic Pathways from Essential Fatty Acids to Prostaglandins



Source: Leson G, Pless P, Roulac J. *Hemp Foods and Oils for Health.* Sebastopol, CA: Hemptech, 1999.

both EFAs. Since these are supplied exclusively with the diet, an imbalance of EFAs in the diet may significantly advance the development of these diseases. Conversely, dietary or therapeutic administration of specific fatty acids will often aid in the prevention, or even treatment of these diseases.

To date, there has been no direct evaluation of the nutritional and health benefits of hemp oil. However, the results of the mentioned studies on FAs and illness, combined with the knowledge of the FA composition of hemp oil suggest that its use as a food oil or a nutritional supplement can be an effective way of preventing and treating certain illnesses. Following is a partial list of illnesses found to respond to treatment with ω-6 and ω-3 fatty acids.

Atopic Eczema (Neurodermitis) and Psoriasis

Patients with atopic eczema suffer from agonizing itching, especially at night. Because of low activity of the sweat and sebaceous glands, the skin feels dry and brittle. Atopic eczema, like psoriasis, is characterized by a higher water loss through the skin. A deficiency in ω-6 polyunsaturated fatty

acids (PUFAs) is associated with these diseases. One potential explanation for this finding is that low enzymatic activity results in slower conversion of linoleic acid to GLA, thus causing a prostaglandin imbalance.

Clinical trials with GLA supplementation have demonstrated gradual improvement in atopic eczema symptoms.[7,23] Patients required considerably fewer anti-itching and antihistamine drugs. Hemp oil, due to its moderate GLA content, may assist in the prevention and treatment of this disease. The daily oral dose found to improve skin conditions over a twelve-week period corresponds to about 20 ml hemp oil per day, which is easily incorporated into the diet.

Omega-6 fatty acids are also involved in regulating water loss through the outer layer of the skin, the epidermis. Skin conditions in atopic eczema patients improved after repeated external application of an ointment containing GLA. The external use of salves and creams containing hemp oil may therefore help maintain the barrier function of the skin, relieve skin itching, and aid in the recovery of atopic eczema patients.

Acne

PUFAs have well-known anti-inflammatory properties, and skin creams containing ω-6 fatty acids have been found effective in the therapeutic treatment of acne skin conditions. Hemp oil's high ω-6 content can therefore be beneficially used in skin-care products for skin of acne patients.

Cardiovascular Disease

Most cardiovascular disease is caused by atherosclerosis. As mentioned, excessive consumption of saturated fatty acids contributes (in addition to lifestyle factors such as smoking and stress) to high blood levels of LDL cholesterol, thus enhancing plaque formation. Dietary treatment of patients with daily doses of linoleic acid and GLA, equivalent to 25 ml hemp oil was shown to rapidly decrease elevated blood levels of both LDL and total cholesterol.[8] Another study showed that consumption of ω-3 fatty acids significantly reduced the risk of sudden cardiac death among survivors of heart attacks.[20] Consequently, the replacement of other dietary oils and fats with hemp oil may help reduce the risk of atherosclerosis and other cardiovascular diseases.

Rheumatoid Arthritis and Other Inflammatory Diseases

GLA and its related prostaglandins have anti-inflammatory and immune system-stimulating properties. Daily oral administration of 1.2 to 1.4 grams of GLA over a period of twelve to twenty-four weeks was found to reduce the symptoms of rheumatoid arthritis significantly without causing side effects.[14,18] Clinical studies have also shown that intake of ω-3 fatty acids has

anti-inflammatory effects in the treatment of chronic bladder infection and inflammatory bowel diseases such as ulcerative colitis and Crohn's disease.

Osteoporosis

Osteoporosis, the gradual decay of the bones with age, is caused by a loss of bone substance, particularly calcium. Back pain, loss of height, kyphosis, and easily fractured bones are its effects. Osteoporosis is usually accompanied by the calcification of arteries and kidneys—a frequent cause of vascular deaths, particularly in women.

Animal studies have shown that EFA deficiency may cause severe osteoporosis. Likewise, dietary supplementation with EFAs increases calcium absorption from the gut, reduces urinary excretion, increases calcium deposition in bones, and enhances bone-collagen synthesis, thereby improving bone strength.[13] Supplementation with GLA was even more effective. Thus, hemp oil, with its moderate content of GLA and well-balanced ratio of EFAs may help to prevent osteoporosis.

PMS and Menopause

PMS, or premenstrual syndrome, affects many women before the onset of their monthly period. It can cause depression, irritability, swelling of the breasts, and painful muscular tension. Studies show that women with PMS suffer from a disorder in the metabolism of fatty acids that also slows the conversion of linoleic acid to GLA and the respective prostaglandins. A daily dose of 150 to 200 milligrams of GLA (corresponding to 5 ml hemp oil) over a twelve-week period significantly improved PMS-related symptoms.[9]

Other Therapeutic Benefits

A dysfunctional fatty acid metabolism also seems to contribute to the following diseases. The potential benefits of EFAs and higher ω-3 and ω-6 fatty acids in their treatment require further study.

Multiple sclerosis (MS), a chronic neurological autoimmune disease, occurs more frequently in northern industrialized countries, where, incidentally, the diet also contains a comparatively low proportion of unsaturated fatty acids.[13] Studies have suggested a link between abnormal EFA metabolism and progression of the MS symptoms, possibly due to a defective enzyme system. MS patients may be unable to convert EFAs to their respective higher PUFAs. Some studies indicate that dietary supplementation with EFAs or GLA will lead to improvements.[6,15]

Diabetes is a chronic endocrine disease. In juveniles, it is usually associated with a lack of the hormone insulin in the blood. Insulin, which is produced in the pancreas, regulates the uptake of blood sugar (glucose) by tis-

sue cells. In adult diabetes, sufficient insulin may be produced, yet the cells have become resistant to it and do not take up glucose fast enough after a meal. This insulin resistance may cause unusual thirst, fatigue, muscle cramps, and even death. Studies show that daily doses of 360 to 460 mg GLA alleviate tingling or numbness in the feet, a diabetes symptom.[11,22] Evidence shows that insufficient ω-3 intake may be one of the cofactors for the development of diabetes, and that a balanced fatty-acid supply may alleviate its other effects as well.[13]

Compared to healthy tissue, cancer cells are deficient in delta-6-desaturase, the enzyme needed to convert either EFA to higher ω-3 and ω-6 fatty acids. Several of these higher PUFAs, including GLA, have been shown to selectively destroy cancerous cells.[1,4] Other studies also suggest that the administration of these higher PUFAs may in fact slow the progress of common cancers, such as breast and prostate cancer.

Further research on dietary supplementation of EFAs, GLA, and other ω-3 and -6 PUFAs suggests improvements in the treatment of chronic depression, postpartum depression, attention deficit disorder, and schizophrenic psychosis, among other afflictions.

There is no direct evidence of the benefits of hemp oil in the treatment of these diseases. Rather, these benefits may be expected from the presence of moderate quantities of GLA and the comparatively high levels of ALA. As mentioned, the deficiency of this ω-3 fatty acid in the diet of many people in industrialized countries is now increasingly implicated in the genesis of several of those illnesses. The use of hemp oil as dietary oil, rather than a nutritional supplement, improves ALA supply and will aid in their prevention.

BODY CARE

In addition to its use for food, hemp oil is increasingly found in body care products, such as soaps, body cream, lotions, shampoos, and shower gels. Its high PUFA content offers excellent emollient and lubricant properties. Applied externally, PUFAs also alleviate dry skin problems and compensate for the effects of skin aging.

Despite these benefits, the use of hemp oil in food and body care applications is expanding only gradually. Among the obstacles it faces, two are worth mentioning.

The THC Issue

Particularly in North America, the use of hemp seeds and oil for human consumption faces an additional obstacle related to the presence of minute quantities of Δ^9-tetrahydrocannabinol (THC), the main psychoactive ingredient of marijuana. The meat of hemp seeds contains only minute amounts of THC (usually less than 0.5 parts per million [ppm]). These compounds

are primarily present in the resinous flowers, sticking to the outside of the hulls, and may be transferred into the oil or seed products during processing.

When hemp seeds were reintroduced for human consumption in the mid-1990s, it was not uncommon to find THC levels in hemp oil from Chinese or European seeds in excess of 100 ppm. The mandatory farming of low-THC varieties, i.e., those containing less than 0.3 percent THC in the upper third of the flowering plants, combined with thorough cleaning of the seeds has been effective in reducing THC levels in oil from European and Canadian seeds to typically less than 10 ppm (mg/kg). Hulled seeds contain even less THC, typically below 3 ppm.

The toxicological evidence available to date suggests that such low levels pose no risk of involuntary intoxication or other detrimental health effects. Based on the review of scientific studies, the Swiss government has set a 50-ppm limit for THC in hemp oil and a limit of 5 ppm for other foods. A comprehensive study by the German nova-Institute[17] has evaluated toxicological data on the potential risk caused by the ingestion of THC with oil and other foods. Based on these data, the nova-Institute recommended THC limits somewhat lower than the Swiss ones, ranging from 0.3 ppm for non-alcoholic beverages to 20 ppm for hemp oil. These limits provide an ample margin of safety from psychoactive and other effects, even when hemp foods are consumed in large quantities. The study also suggests that the absorption of THC from hemp oil-based skin care products is not effective and will not cause any relevant uptake. A summary of the study is available at the Web site of the North American Industrial Hemp Council (www.naihc.org).

In the United States, the extensive testing of employees for potential abuse of marijuana has created an additional concern over THC residues in hemp seed products. Very limited tests conducted in 1995-1997 suggested that the consumption of hemp oil may in fact produce THC metabolites in urine in excess of the 50 parts per billion (ppb) cutoff commonly used for immunoassay screening tests. However, these tests were conducted with then commercially available hemp seed products containing relatively high THC levels—likely imported from China. A correlation between consumption of hemp seed oil and THC metabolites in urine was established in a Canadian study. Results suggest that an ingestion of up to 0.45 mg THC/day of THC is not likely to produce positives at the 50 ppb cutoff for screening tests, nor at the commonly associated 15 ppb cutoff used to confirm these results with GC/MS (gas chromatography/mass spectrometry). The amount of hemp foods required to ingest 0.45 mg of THC correspond to about 225 g hulled hemp seeds (2 μg THC/g) or about 50 ml hemp seed oil (10 μg/g), quantities which are not impossible, yet also not likely to be consumed. Thus, even people who frequently consume hemp foods of the quality now found in stores will not fail urine tests for marijuana—as long as seed pro-

cessors consistently keep THC levels in hemp oil and hulled seeds below 5 and 2 ppm and employers and laboratories follow generally accepted practices for evaluating urine samples, i.e., routine confirmation of positive screening tests with GC/MS.[12]

Hemp Seeds

In addition to hemp oil, hulled hemp seeds are now emerging as ingredients for food products in Europe and North America. These hulled seeds, or hemp nuts, also contain about 35 percent protein; 65 percent of the total protein occurs as the easily digestible storage protein edestin. Limited data on their amino acid spectrum indicates that hemp seed proteins contain all nine essential amino acids and feature a high content of the sulfur-containing amino acids methionine and cysteine, usually underrepresented in vegetable proteins. Yet, because of its low content of the essential amino acid lysine, hemp seed protein, like most vegetable proteins, cannot be considered complete.

Proteins are potential allergens for the human body, including soy, whey, or peanut protein. So far, no allergies to hemp protein have been reported. Several oilseeds also contain antinutritional factors, such as trypsin inhibitors in soybeans. None of these factors are known to occur in hemp seeds. They also contain fewer oligosaccharides present in peas and beans, which cause intestinal gases.

The combination of beneficial fatty acid and amino acid spectra their pleasant nutty taste, and their versatility, qualify hemp seeds and hemp oil as raw materials with a considerable potential in the natural foods market. However, the removal of the aforementioned obstacles is a prerequisite for the utilization of this potential.

REFERENCES

1. Begin ME, Das UN, Ells G, Horrobin DF. Selective killing of human cancer cells by polyunsaturated fatty acids. *Prostaglandins, Leukotrienes, and Medicine* 1985;19:177-186.

2. Bokisch M. *Fats and oils handbook*. Champaign, IL: AOCS Press, 1998.

3. Cunnane SC, Thompson LU, eds. *Flaxseed in human nutrition*. Champaign, IL: AOCS Press, 1995.

4. Dippenaar N, Booyens J, Fabbri D, Engelbrecht P, Katzeff IE. The reversibility of cancer: Evidence that malginancy in human hepatoma cells is gamma-linolenic acid deficiency dependent. *South African Medical Journal* 1982; 62(19):683-685.

5. Erasmus U. *Fats that Heal, Fats that Kill*. Vancouver, Canada: Alive Books, 1994.

6. Field EJ. Gamma-linenolate in multiple sclerosis. *Lancet* 1978;1(8067):780.

7. Fiocchi A, Sala M, Signoroni P, Banderali G, Agostini C, Riva E. The efficacy and safety of gamma-linolenic acid in the treatment of infantile atopic dermatitis. *Journal of International Medical Research* 1994;22(1):24-32.

8. Guivernau M, Meza N, Barja P, Roman O. Clinical and experimental study on the long-term effect of dietary gamma-linolenic acid on plasma lipids, platelet aggregation thromboxane formation, and prostacyclin production. *Prostaglandins Leukotrienes and Essential Fatty Acids* 1994;51(5):311-316.

9. Horrobin DF, Manku MS. Premenstrual syndrome and premenstrual breast pain (Cyclical Mastalgia): Disorders of essential fatty acid (EFA) metabolism. *Prostaglandins Leukotrienes and Essential Fatty Acids* 1989;37(4):255-262.

10. Huang Y-S, Mills DE, eds. *Gamma-linolenic acid: Metabolism and its roles in nutrition and medicine*. Champaign, IL: AOCS Press, 1995.

11. Jamal GA. The use of gamma-linolenic acid in the prevention and treatment of diabetic neuropathy. *Diabetic Medicine* 1994;11(2):145-149.

12. Leson G, Pless P, Grotenhermen F, Kalant H, ElSohly MA. Evaluating the Impact of Hemp Food Consumption in Workplace Drug Tests. *Journal of Analytical Toxicology* 2001, in press.

13. Leson G, Pless P, Roulac J. *Hemp foods and oils for health*. Sebastopol, CA: Hemptech, 1999.

14. Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with gamma-linolenic acid. *Annals of Internal Medicine* 1993;119(9):867-873.

15. Meyer-Rienekerck HJ, Jenssen HL, Kohler H, Field EJ, Shenion BK. Effect of gamma-linenolate on multiple sclerosis. *Lancet* 1976;2(7992):966.

16. Nova-Institute, ed. *Hanfsamen und Hanföl als Lebens- und Heilmittel*. [Hemp seed and hemp oil as food and remedy.] Göttingen: Verlag die Werkstatt, 1998.

17. nova-Institute, ed. *Hemp foods and THC levels*. Sebastopol, CA: Hemptech, 1998.

18. Pullman-Mooar S, Laposata M, Lem D, Holman RT, Leventhal LJ, DeMarco D, Zurier RB. Alterations of the cellular fatty acid profile on the production of eicosanoids in human monocytes by gamma-linolenic acid. *Arthritis and Rheumatism* 1990;33(10):1526-1533.

19. Rudin DO, Felix C. *Omega-3 oils: To improve mental health, fight degenerative diseases, and extend your life*. New York: Avery Publishing Group, 1996.

20. Sellmeyer A, Witzgall H, Lorenz R, Weber PC. N-3 Fettsäuren: Natürliche Antiarrhythmika? [N-3 fatty acids. Natural antiarrhythmics?] *Deutsches Ärzteblatt* 1996;93:2145-2148.

21. Simopoulos A, Robinson J. *The omega diet*. New York: Harper Perennial, 1999.

22. The Gamma-Linolenic Acid Multicenter Trial Group. Treatment of diabetic neuropathy with gamma-linolenic acid. *Diabetes Care* 1993;16:8-15.

23. Wright S, Burton JL. Oral evening primrose oil improves atopic eczema. *Lancet* 1982;2(8308):1120-1122.

Resources

International Association for Cannabis As Medicine (IACM)

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http://www.cannabis-med.org

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