Clinical Pharmacodynamics of Cannabinoids

Franjo Grotenhermen

ABSTRACT. Our knowledge of the pharmacodynamics of cannabinoids, that is, "the study of the biochemical and physiologic effects of drugs and their mechanisms of action" (*The Merck Manual*), has considerably increased within the past decade due to the detection of an endogenous cannabinoid system with specific receptors and their endogenous ligands.

THC (Δ^9-tetrahydrocannabinol), the main source of the pharmacological effects caused by the use of cannabis including the medicinal benefits of the plant, is an agonist to both the CB_1 and the CB_2 subtype of these receptors. Its acid metabolite THC-COOH (11-nor-9-carboxy-THC), the non-psychotropic cannabidiol (CBD), analogues of these natural compounds, antagonists at the cannabinoid receptors and modulators of the endogenous cannabinoid system are also promising candidates for clinical research and therapeutic uses. Cannabinoid receptors are distributed in the central nervous system and many peripheral tissues (spleen, leukocytes; reproductive, urinary and gastrointestinal tracts; endocrine glands, arteries and heart, etc.). Additionally, there is evidence for non-receptor dependent mechanisms of cannabinoids.

Five endogenous cannabinoids, anandamide, 2-arachidonylglycerol, noladine ether, virodhamine, and NADA, have been detected. There is evidence that besides the two cannabinoid receptor subtypes cloned so far, additional cannabinoid receptor subtypes and vanilloid receptors are involved in the complex physiological functions of endocannabinoids that include, for example, motor coordination, memory procession, pain modulation and neuroprotection. Strategies to modulate their activity include inhibition of re-uptake into cells and inhibition of their degradation to increase concentration and duration of action.

Franjo Grotenhermen, MD, is affiliated with the nova-Institut, Goldenbergstraße 2, D-50354 Hürth, Germany (E-mail: franjo-grotenhermen@nova-institut.de).

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At doses exceeding the psychotropic threshold, ingestion of exogenous CB_1 receptor agonists or cannabis, respectively, usually causes an enhanced well-being and relaxation with an intensification of ordinary sensory experiences. The most important potential adverse acute effects caused by overdosing are anxiety and panic attacks, and with regard to somatic effects, increased heart rate and changes in blood pressure. Regular use of cannabis may lead to dependency and to a mild withdrawal syndrome. The existence and the intensity of possible long-term damages on psyche and cognition, immune system, fertility and on pregnancy remain controversial. They are reported to be low in humans and do not preclude a legitimate therapeutic use of cannabis based drugs.

Properties of cannabinoids that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects.

KEYWORDS. Cannabis, THC, cannabinoids, marijuana, pharmacodynamics, cannabinoid receptors, endocannabinoids, mechanism of action, therapeutic use, therapeutic potential, side effects, interaction

INTRODUCTION

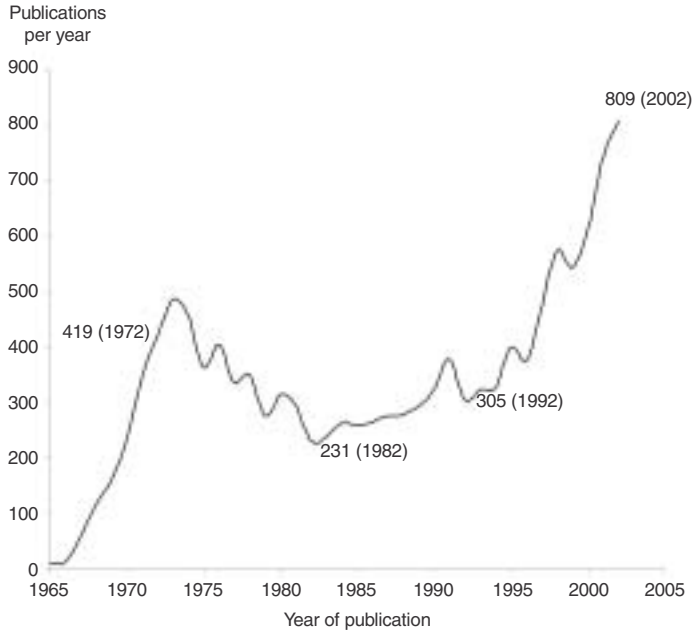
Unlike the opiates and many other medicinally used plant constituents, the cannabinoids were not identified before the 20th century, which occasionally resulted in dosing problems of oral medicinal extracts which had been in use in the 19th century in Europe and North America. In the 1930s and 1940s, the chemical structure of the first phytocannabinoids had been successfully characterized (Loewe 1950), and the first synthetic derivatives of THC (parahexyl, DMHP) were successfully tested in clinical studies for epilepsy (Davis and Ramsey 1949), depression (Stockings 1947) and dependency to alcohol and opiates (Thompson and Proctor 1953). However, it was not until 1964 that Δ^9-tetrahydrocannabinol (Δ^9-THC, dronabinol), mainly responsible for the pharmacological effects of the cannabis plant (Dewey 1986, Hollister 1986), was stereochemically defined, and synthesized (Gaoni and Mechoulam 1964). Another scientific breakthrough in cannabinoid

research was the detection of a system of specific cannabinoid receptors in mammals and their endogenous ligands within the past 15 years. Both detections resulted in a considerable boost in research activities (see Figure 1).

Cannabinoids were originally thought to be only present in the cannabis plant (*Cannabis sativa* L.), but recently some cannabinoid type bibenzyls have also been found in liverwort (*Radula perrottetii* and *Radula marginata*) (Toyota et al. 2002), the chemical structure of perrottetinenic acid in liverwort being similar to that of Δ^9-THC in cannabis.

About 65 cannabinoids have been detected in the cannabis plant, mainly belonging to one of 10 subclasses or types (ElSohly 2002), of which the cannabigerol type (CBG), the cannabichromene type (CBC), the cannabidiol type (CBD), the Δ^9-THC type (with nine cannabinoids), and the cannabinol type (CBN) are the most relevant in quantity. Cannabinoid distribution varies between different cannabis strains and

FIGURE 1. Dynamic of cannabinoid publications. Annual number of publications found in PubMed (http://www.ncbi.nlm.nih.gov/PubMed/) by using the keywords "cannabis, cannabinoids, THC, marijuana" between 1965 and 2002.



usually only three or four cannabinoids are found in one plant in relevant concentrations. Other cannabis compounds of possible pharmacological interest are terpenes (about 120) which are responsible for the specific smell of the plant, flavonoids (21), and nitrogenous compounds (27) including two spermidine type alkaloids.

Δ^9-THC, the main cannabinoid in cannabis of the drug type with concentrations in a range between 2 and 30% in the flowering tops and upper leaves of the female plant, given alone produced similar effects as whole plant drug cannabis (marijuana) in healthy volunteers (Hart et al. 2002, Wachtel et al. 2002) and patients (Abrams et al. 2001). In one study, pure THC and whole cannabis were either smoked or taken orally in a double-blind, crossover design with five experimental conditions: a low and a high dose of THC-only, a low and a high dose of whole-plant cannabis, and placebo (Wachtel et al. 2002). In both the oral study and the smoking study, THC-only and whole plant cannabis produced similar subjective effects, with only minor differences. The THC main effects, including medicinal properties, may be modulated by other cannabinoids, mainly CBD, and other cannabis constituents (McPartland and Russo 2001).

In addition to these phytocannabinoids, synthetic agonists and antagonists at the cannabinoid receptor and other modulators of the endogenous cannabinoid system are under investigation for therapeutic purposes.

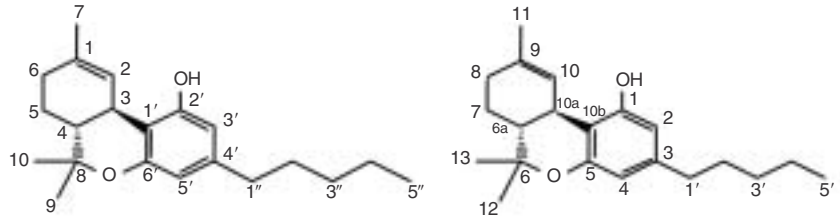
MECHANISM OF ACTION

The mechanism of action of cannabinoids is best investigated for Δ^9-THC (THC, dronabinol; see Figure 2 for chemical structure) and other cannabinoid receptor agonists, while the mode of action of other cannabinoids of therapeutic interest, among them CBD, as well as the carboxy metabolite of THC (11-nor-9-carboxy-Δ^9-THC) and its analogues (e.g., ajulemic acid, CT-3) is less well established. Previous reviws on cannabis include two by Grotenhermen (2002b,c).

Mechanism of Action of Δ^9-THC

The majority of THC effects are mediated through agonistic actions at cannabinoid receptors. Some non-CB mediated effects of THC and synthetic derivatives have also been described, e.g., some effects on the immune system (Bueb et al. 2001), some neuroprotective effects (Hampson

FIGURE 2. Chemical structure of THC, the main cannabinoid in the cannabis plant, according to the monoterpenoid system (Δ^1-THC) and dibenzopyran system (Δ^9-THC).



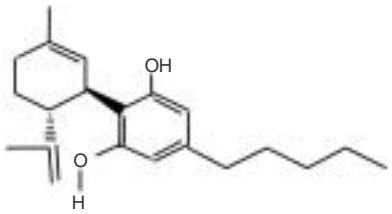
2002), and anti-emetic effects. The anti-emetic effects of THC are supposed to be mediated in part by CB_1 receptors (Parker et al. 2003) and in part by non-CB mechanisms, the rationale for the clinical use of THC as an anti-emetic in children receiving cancer chemotherapy (Abrahamov et al. 1995). Due to the lower CB_1 receptor density in the brain of children compared with adults, they tolerated relatively high doses of Δ^8-THC in a clinical study, without significant CB_1 receptor mediated adverse effects (Abrahamov et al. 1995). In a study with cells stably transfected with the human 5-HT_{3A} receptor, several (endo)cannabinoids (THC, WIN55,212-2, anandamide, etc.) directly inhibited currents induced by 5-hydroxytryptamine (Barann et al. 2002). Since 5-HT_3 antagonists are potent anti-emetic drugs, this may be one mechanism by which cannabinoids act as anti-emetics.

It is possible that several effects previously thought to be non-receptor mediated are mediated by cannabinoid receptor subtypes that have not yet been identified.

Mechanism of Action of Cannabidiol

The mode of action of cannabidiol (see Figure 3 for chemical structure) is not fully understood and several mechanisms have been proposed: (1) CBD acts as antagonist at the central CB_1 receptor and is able to inhibit several CB_1 mediated THC effects (Zuardi et al. 1982). In a study by Petitet et al. (1998), CBD considerably reduced the receptor activation by the potent classical CB_1 receptor agonist CP55940. (2) CBD stimulates the vanilloid receptor type 1 (VR_1) with a maximum effect similar in efficacy to that of capsaicin (Bisogno et al. 2001).

FIGURE 3. Cannabinoid.



(3) CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration (Bisogno et al. 2001, Mechoulam and Hanus 2002). (4) Finally, CBD may also increase the plasma THC level (Bornheim et al. 1995) by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system (Bornheim et al. 1998, Jaeger et al. 1996). However, there was no or minimal effect of CBD on plasma levels of THC in man (Agurell et al. 1981, Hunt et al. 1981).

In a study that analyzed the mode of action of the anti-inflammatory and anti-hyperalgesic effects of CBD, simultaneous administration of a VR_1 receptor antagonist fully reversed the anti-hyperalgesic effects (Costa et al. 2003). A CB_2 receptor antagonist was partly effective and a CB_1 receptor antagonist had no effect. The anti-inflammatory efficacy of CBD was unrelated to cyclooxygenase (COX) activity, but inhibited the endothelial isoform of nitric oxide synthase (eNOS). In a rat model of arthritis, low doses of CBD decreased prostaglandin E_2, nitric oxide and lipid peroxide level, mediators that are all known to be involved in the development and maintenance of arthritis (Costa et al. 2003).

CANNABINOID RECEPTORS

To date two cannabinoid receptors have been identified, the CB_1 (cloned in 1990), and the CB_2 receptor (cloned in 1993) (Pertwee 1997), exhibiting 48% amino acid sequence identity. Besides their difference in amino acid sequence, they differ in signaling mechanisms, tissue distribution, and sensitivity to certain agonists and antagonists that show marked selectivity for one or the other receptor type (Howlett et al. 2002). Both receptor types are coupled through inhibiting G proteins (G_i proteins), negatively to adenylate cyclase, and positively to mito-

gen-activated protein kinase. Activation of G_i proteins causes inhibition of adenylate cyclase, thus, inhibiting the conversion of ATP to cyclic AMP (cAMP). CB_1 receptors are also coupled to certain kinds of calcium channels and potassium channels (Pertwee 2002). They may also mobilize arachidonic acid and close 5-HT_3 receptor ion channels (Pertwee 2002). Under certain conditions, they may also activate adenylate cyclase through stimulating G proteins (G_s proteins) (Glass and Felder 1997).

CB_1 receptors are mainly found on neurons in the brain, spinal cord and peripheral nervous system, but are also present in certain peripheral organs and tissues, among them endocrine glands, leukocytes, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts (Pertwee 1997). In the central nervous system the CB_1 receptor is the most abundant G-protein coupled receptor. One of its functions is inhibition of neurotransmitter release. Their endogenous agonists probably serve as retrograde synaptic messengers. CB_1 receptors are highly expressed in the basal ganglia, cerebellum, hippocampus and dorsal primary afferent spinal cord regions, which reflect the importance of the cannabinoid system in motor control, memory processing and pain modulation, while their expression in the brainstem is low (Howlett et al. 2002), which may account for the lack of cannabis-related acute fatalities, e.g., due to depression of respiration.

CB_2 receptors occur principally in immune cells, among them leukocytes, spleen and tonsils (Pertwee 2002). In contrast to CB_1 receptors they are not coupled to ion channels. Immune cells also express both CB_1 receptors but there is markedly more mRNA for CB_2 than CB_1 receptors in the immune system. 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) (Galiègue et al. 1995). One of the functions of CB receptors in the immune system is modulation of cytokine release.

Activation of the CB_1 receptor produces marijuana-like effects on psyche and circulation, while activation of the CB_2 receptor does not. Hence, selective CB_2 receptor agonists have become an increasingly investigated target for therapeutic uses of cannabinoids, among them analgesic, anti-inflammatory and anti-neoplastic actions (Recht et al. 2001, Sanchez et al. 2001).

There is increasing evidence for the existence of additional cannabinoid receptor subtypes in the brain and periphery (Breivogel et al. 2001, Di Marzo et al. 2000, Fride et al. 2003, Wiley and Martin 2002). These receptors are more likely to be functionally related to the known

cannabinoid receptors than have a similar structure as there is no evidence for additional cannabinoid receptors in the human genome (Baker et al. 2003).

ENDOCANNABINOIDS

The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, endogenous cannabinoids or endocannabinoids, a family of eicosanoids (Devane et al. 1992, Giuffrida et al. 2001, Sugiura et al. 1995). To date five endocannabinoids have been identified. These are *N*-arachidonylethanolamide (anandamide) (Devane et al. 1992), 2-arachidonylglycerol (2-AG) (Mechoulam et al. 1995, Sugiura et al. 1995), 2-arachidonylglyceryl ether (noladin ether) (Hanus et al. 2001), *O*-arachidonyl-ethanolamine (virodhamine) (Porter et al. 2002), and *N*-arachidonyl-dopamine (NADA) (Huang et al. 2002).

Cannabinoid receptors and their endogenous ligands together constitute the "endogenous cannabinoid system," or the "endocannabinoid system" which is teleologically millions of years old and has been found in mammals and many other species (De Petrocellis et al. 1999).

Endocannabinoids serve as neurotransmitters or neuromodulators (Howlett 2002). Anandamide and NADA do not only bind to cannabinoid receptors but also stimulate vanilloid receptors (VR_1) (Al-Hayani et al. 2001, Huang et al. 2002), non-selective ion channels associated with hyperalgesia. Thus, the historical designation of anandamide as an "endocannabinoid" seems to be only one part of the physiological reality, and cannabinoid receptors seem to amount only to some of the "anandamide receptors." Some non CB effects may be mediated by vanilloid receptors, e.g., inhibition of cell proliferation of rat C6 glioma cells by endocannabinoids was reported to involve combined activation of both vanilloid receptors and to a lesser extent cannabinoid receptors (Jacobsson et al. 2001).

The first two discovered endocannabinoids, anandamide (Figure 4) and 2-AG (Figure 5), are the best to be studied. They are produced "on demand" by cleavage of membrane lipid precursors and released from cells in a stimulus-dependent manner (Giuffrida et al. 2001). The production of anandamide and 2-AG involves phospholipases D and C. After release, they are rapidly deactivated by uptake into cells and metabolized. Metabolism of anandamide and 2-AG occurs by enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) (Di Marzo 1998, Giuffrida

FIGURE 4. Arachidonylethanolamide (anandamide).

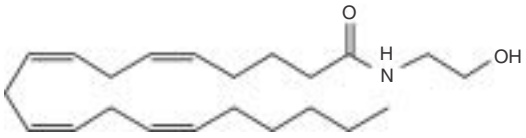
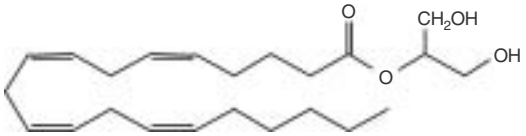


FIGURE 5. 2-Arachidonylglycerol (2-AG).



et al. 2001). FAAH degrades anandamide to arachidonic acid and ethanolamide. In mice, lack of FAAH resulted in supersensitivity to anandamide and enhanced endogenous cannabinoid signalling (Cravatt et al. 2001). Other metabolic processes include hydrolysis of 2-AG by monoglyceride lipase (Dinh et al. 2002), acylation of noladin ether (Fezza et al. 2002), oxidation of anandamide and 2-AG and methylation of the aromatic moiety of NADA.

In all cases cellular uptake must preceed metabolism since metabolism occurs only in the cells. Endocannabinoid uptake by cells seems to happen by "enhanced diffusion" through the cell membrane (Fowler and Jacobsson 2002, Huang et al. 2002, Porter et al. 2002), even though an active carrier system has not been detected so far. Simple passive diffusion following a concentration gradient into the cells, where they are quickly metabolized by FAAH, is regarded as unlikely, since several substances have been developed that are thought to inhibit anandamide cellular uptake without inhibiting FAAH, among them Arvanil (Di Marzo et al. 2002) and VDM11 (Baker et al. 2001), and noladine ether and NADA are rapidly taken up into cells despite they are rather stable or refractory to enzymatic hydrolysis (Fezza et al. 2002, Huang et al. 2002). However, the discussion on the existence of a transport system is not finished, and one group demonstrated that arvanil and other substances regarded as anandamide transporters (olvanil, AM404) were actually inhibitors of FAAH (Glaser et al. 2003). Intracellular uptake of endocannabinoids is a temperature dependent and rapid process with a

half time of a few minutes, compared to hours in the case of exogenous plant cannabinoids.

AFFINITY TO THE CANNABINOID RECEPTOR

Cannabinoids show differing affinities for CB_1 and CB_2 receptors. Synthetic cannabinoids have been developed that act as highly selective agonists or antagonists at one of these receptor types (Abadji et al. 1994, Pertwee 1999b, Pertwee 2002). Δ^9-THC has approximately equal affinity for the CB_1 and CB_2 receptor, while anandamide has marginal selectivity for CB_1 receptors (Pertwee 1999b). However, the efficacy of THC and anandamide is less at CB_2 than at CB_1 receptors. In contrast to the anandamide, 2-AG and noladine ether which act as agonists at both CB receptor types, virodhamine acts as an antagonist at the CB_1 receptor and as a full agonist at the CB_2 receptor (Porter et al. 2002).

TONIC ACTIVITY OF THE ENDOCANNABINOID SYSTEM

When administered by themselves, cannabinoid receptor antagonists may behave as inverse agonists in several bioassay systems, i.e., not only block the effects of exogenous cannabinoids but produce effects that are opposite in direction from those produced by cannabinoid receptor agonists, e.g., cause hyperalgesia (Jaggar 1998), suggesting that the endogenous cannabinoid system is tonically active. Tonic activity may be due to a constant release of endocannabinoids or from a portion of cannabinoid receptors that exist in a constitutively active state (Pertwee 2002).

Tonic activity of the endogenous cannabinoid system has been demonstrated in several conditions. Endocannabinoids have been shown to be tonically active in the dorsal horn neurons of the spinal cord, thus, attenuating acute nociceptive transmission at the level of the spinal cord (Chapman 1999). Endocannabinoid levels have been demonstrated to be increased in a pain circuit of the brain (periaqueductal gray) following painful stimuli (Walker et al. 1999). Tonic control of spasticity by the endocannabinoid system has been observed in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice, an animal model of multiple sclerosis (Baker et al. 2001). An increase of cannabinoid receptors following nerve damage was demonstrated in a

rat model of chronic neuropathic pain (Siegling et al. 2001) and in a mouse model of intestinal inflammation (Izzo et al. 2001). This may increase the potency of cannabinoid agonists used for the treatment of these conditions. Tonic activity has also been demonstrated with regard to appetite control (Di Marzo et al. 2000b) and with regard to vomiting in emetic circuits of the brain (Darmani 2001). Elevated endocannabinoid levels have been detected in cerebrospinal fluid of schizophrenic patients (Leweke et al. 1999). In other models tonic or enhanced activity could not be demonstrated, e.g., in a rat model of inflammatory hyperalgesia (Beaulieu et al. 2000).

PHARMACOLOGICAL EFFECTS OF THC

The pharmacological activity of Δ^9-THC is stereoselective, with the natural (−)-trans isomer (dronabinol) being 6-100 times more potent than the (+)-trans isomer, depending on the assay (Dewey 1986).

The activation of the cannabinoid system through THC and other phytocannabinoids, synthetic and endogenous cannabinoids causes numerous actions that have been extensively reviewed (see Table 1) (Adams and Martin 1996, Dewey 1986, Grotenhermen and Russo 2002, Hall et al. 1994, Hollister 1986, House of Lords 1998, Joy et al. 1999, Kalant et al. 1999). Additional non-receptor mediated effects have come into focus as well (Hampson 2002). Some effects of cannabinoid receptor agonists show a biphasic behavior in dependency of dose, e.g., low doses of anandamide stimulated phagocytosis and stimulated behavioral activities in mice while high doses decreased activities and caused inhibitory effects on immune functions (Sulcova et al. 1998).

TOXICITY

The median lethal dose (LD_{50}) of oral THC in rats was 800-1900 mg/kg depending on sex and strain (Thompson et al. 1973). There were no cases of death due to toxicity following the maximum oral THC dose in dogs (up to 3000 mg/kg THC) and monkeys (up to 9000 mg/kg THC) (Thompson et al. 1973). Acute fatal cases in humans have not been substantiated. However, myocardial infarction may be triggered by THC due to effects on circulation (Bachs and Morland 2001, Mittleman et al. 2001). However, this is unlikely to occur in healthy subjects, but possibly

TABLE 1. Effects of THC. The Following Dose-Dependent Effects Were Observed in Clinical Studies, *in vivo*, or *in vitro*

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, aggravation of psychotic states, sleep.
Cognition and psychomotor performance. Fragmented thinking, enhanced creativity, disturbed memory, unsteady gait, ataxia, slurred speech, weakness, deterioration or amelioration of motor coordination.
Nervous system. Analgesia, muscle relaxation, appetite stimulation, vomiting, anti-emetic effects, neuroprotection in ischemia and hypoxia.
Body temperature. Decrease of body temperature.
Cardiovascular system. Tachycardia, enhanced heart activity, increased output, 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, immune stimulation, anti-inflammatory and anti-allergic 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.

in persons with coronary heart disease for whom orthostatic hypotension or a moderately increased heart rate may pose a risk.

Adverse effects of medical cannabis use are within the range of effects tolerated for other medications (House of Lords 1998, Joy et al. 1999). It is controversial whether heavy regular consumption may impair cognition (Pope et al. 2001, Pope 2002, Solowij et al. 2002), but this impairment seems to be minimal if it exists (Lyketsos et al. 1999, Pope et al. 2001). Early users who started their use before the age of 17 presented with poorer cognitive performance, especially verbal IQ compared to users who started later or non-users (Pope et al. 2003). Possible reasons for this difference may be (1) innate differences between groups in cognitive ability, antedating first cannabis use; (2) a neurotoxic

effect of cannabis on the developing brain; or (3) poorer learning of conventional cognitive skills by young cannabis users who have eschewed school and university (Pope et al. 2003).

Long-term medical use of cannabis for more than 15 years has been reported to be well-tolerated without significant physical or cognitive impairment (Russo et al. 2002). There is conflicting evidence that infants exposed to THC *in utero* suffer developmental and cognitive impairment (Fried et al. 1998). Marihuana can induce a schizophrenic psychosis in vulnerable persons (Hall et al. 1994, Solowij and Grenyer 2002b) and there is increasing evidence that there is a distinct cannabis psychosis (Nunez and Gurpegui 2002).

The harmful effects of combustion products produced by smoking cannabis have to be distinguished from effects by cannabis or single cannabinoids (Joy et al. 1999).

PSYCHE, COGNITION AND BEHAVIOR

In many species the behavioral actions of low doses of THC are characterized by an unique mixture of depressant and stimulant effects in the CNS (Dewey 1986).

In humans, THC or cannabis consumption is usually described as a pleasant and relaxing experience. Use in a social context may result in laughter and talkativeness. Occasionally there are unpleasant feelings such as anxiety that may escalate to panic. A sense of enhanced well-being may alternate with dysphoric phases. THC improves taste responsiveness and enhances the sensory appeal of foods (Mattes et al. 1994). It may induce sleep (Freemon 1972, Lissoni et al. 1986).

Acute THC intoxication impairs learning and memory (Hampson and Deadwyler 1999, Heyser et al. 1993, Slikker et al. 1992), and may adversely affect psychomotor and cognitive performance (Solowij and Grenyer 2002b), reducing the ability to drive a car and to operate machinery. Reduced reaction time also affects the response of the pupil of the eye. A brief light flash shows decreased amplitude of constriction and a decelerated velocity of constriction and dilation (Kelly et al. 1993).

The most conspicuous psychological effects of THC in humans have been divided into four groups: 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) (Perez-Reyes 1999).

These effects only appear if an individually variable threshold of dose is exceeded. During a study on the efficacy of dronabinol (THC) in 24 patients with Tourette syndrome who received up to 10 mg THC daily for 6 weeks, no detrimental effects were seen on neuropsychological performance (learning, recall of word lists, visual memory, divided attention) (Müller-Vahl et al. 2003a).

CENTRAL NERVOUS SYSTEM AND NEUROCHEMISTRY

Most THC effects (analgesia, appetite enhancement, muscle relaxation, hormonal actions, etc.) are mediated by central cannabinoid receptors, their distribution reflecting many of the medicinal benefits and side effects (Hampson and Deadwyler 1999, Pertwee 2002, Sañudo-Peña et al. 1999).

Cannabinoids interact with a multitude of neurotransmitters and neuromodulators (Dewey 1986, Pertwee 1992), among them acetylcholine, dopamine, α-aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptides (see Table 2). 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 (Domino 1999, Mattes et al. 1994) are mediated by effects of THC on release and turn-over of acetylcholine (Domino 1999). In a rat model, cannabinoid agonists inhibited activation of 5-HT_3 receptors, explaining antiemetic properties of cannabinoids to be based on interactions with serotonin (Fan 1995). Therapeutic effects in movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutamergic and dopaminergic transmitters systems (Müller-Vahl et al. 2002b, Musty and Consroe 2002).

Cannabinoids influence the activity of most neurotransmitters in a complex manner, which sometimes may result in contradictory effects with suppression or induction/intensification of convulsion, emesis, pain and tremor depending on subject and condition. Cannabis and dronabinol are used against nausea and vomiting caused by anti-neoplastic drugs but rarely may cause vomiting. They are used as analgesics but sometimes may increase pain, etc. These observations are probably based on the control of these effects by several neuronal circuits influenced by cannabinoids. Influence on neurotransmitters may depend on brain region. Thus, dopamine activity may be reduced by cannabinoids in brain areas responsible for motor control (Giuffrida et

TABLE 2. Neurotransmitter Functions Under Cannabinoid Control (Modified According to Baker et al. 2003)

Neurotransmitter	Associated disorder
Excitatory amino acids	
Glutamate	Epilepsy, nerve-cell death in ischemia and hypoxia (stroke, head trauma, nerve gas toxicity)
Inhibitory amino acids	
GABA	Spinal cord motor disorders, epilepsy, anxiety
Glycine	Startle syndromes
Monoamines	
Noradrenaline	Autonomic homeostasis, hormones, depression
Serotonin	Depression, anxiety, migraine, vomiting
Dopamine	Parkinson's disease, schizophrenia, vomiting, pituitary hormones, drug addiction
Acetylcholine	Neuromuscular disorders, autonomic homeostasis (heart rate, blood pressure), dementia, parkinsonism, epilepsy, sleep-wake cycle
Neuropeptides	Pain, movement, neural development, anxiety

al. 1999) but enhanced in the reward system (Gardner 2002). Interactions of cannabinoids with other neurotransmitter systems may cause unexpected effects. While studies in animals have demonstrated that opioid receptor antagonists precipitated a cannabinoid-like withdrawal syndrome in cannabinoid-dependent rats (Lichtman et al. 2001) and blocked other effects related to behavioral effects of CB_1 agonists (Braida et al. 2001, Tanda et al. 1997), in humans opioid receptor antagonists did not block the subjective effects of THC in one study (Wachtel and de Wit 2000) or even increased the subjective effects THC in another study (Haney et al. 2003).

One important physiological role of endocannabinoids seems to be neuroprotection (Mechoulam 2002). Ischemia and hypoxia in the CNS induce abnormal glutamate hyperactivity and other processes that cause neuronal damage. These processes also play a role in chronic neurodegenerative diseases such as Parkinson's and Alzheimer's disease and

multiple sclerosis. Neuroprotective mediators are also released in ischemia and hypoxia, including anandamide and 2-AG. When these two cannabinoids were administered after traumatic brain injury in animals, they reduced brain damage (Mechoulam 2002). Neuroprotective cannabinoid mechanisms observed in animal studies include reduction of glutamate toxicity by inhibition of excessive glutamate production, inhibition of calcium influx into cells, anti-oxidant properties which reduce damage caused by oxygen radicals and modulation of vascular tone (Grundy 2002, Hampson 2002, Mechoulam 2002). THC was neuroprotective in rats given the toxic agent ouabain. THC treated animals showed reduced volume of edema by 22% in the acute phase and 36% less nerve damage after 7 days (van der Stelt et al. 2001). Whether these effects may be of therapeutic benefit in acute or chronic diseases has to be elucidated. Clinical studies under way investigating the therapeutic potential of a non-psychotropic derivative of THC in acute conditions (head trauma, stroke and nerve gas intoxication) showed initial positive results (Knoller et al. 2002).

CIRCULATORY SYSTEM

THC can induce tachycardia (Perez-Reyes 1999) and increase cardiac output with increased cardiac labor and oxygen demand (Tashkin et al. 1977). It can also produce peripheral vasodilation, orthostatic hypotension (Benowitz and Jones 1975, Hollister 1986) and reduced platelet aggregation (Formukong et al. 1989). There was no change of mean global cerebral blood flow after smoking cannabis but increases and decreases in several regions (O'Leary et al. 2002).

In young healthy subjects the heart is under control of the vagus which mediates bradycardia. Tachycardia by THC may easily be explained by vagal inhibition (inhibited release of acetylcholine) through presynaptic CB_1 receptors (Szabo et al. 2001), which can be attenuated by beta-blockers (Perez-Reyes 1999) and blocked by the selective CB_1 antagonist SR141716A (Huestis et al. 2001). Regular use can lead to bradycardia (Benowitz and Jones 1975). The endogenous cannabinoid system seems to play a major role in the control of blood pressure. Hypotension is mediated by central inhibition of the sympathetic nervous system, obviously by activation of CB_1 receptors since this effect can also be prevented by a CB_1 antagonist (Lake et al. 1997). Endocannabinoids are produced by the vascular endothelium, circulating macrophages and platelets (Wagner et al. 1998). Vascular resistance in

the coronaries and the brain is lowered primarily by direct activation of vascular cannabinoid CB_1 receptors (Wagner et al. 2001).

SOME OTHER ORGAN SYSTEMS AND EFFECTS

Antibacterial and antiviral actions. Antibacterial actions have been demonstrated for CBD, CBG and THC (Van Klingeren and Ten Ham 1976). Incubation with THC reduced the infectious potency of herpes simplex viruses (Lancz et al. 1991).

Appetite and eating. The endogenous cannabinoid system plays a critical role in milk ingestion of newborn mice (Fride et al. 2003). Blockade of the CB_1 receptor results in death of newborns in this setting (Fride and Shohami 2002). Anandamide induces overeating in rats through a CB_1 receptor mediated mechanism (Williams and Kirkham 1999). Endocannabinoids in the hypothalamus are part of the brain's complex system for controlling appetite which is regulated by leptin (Di Marzo et al. 2001). Leptin is the primary signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. Leptin reduces food intake by upregulating appetite-reducing neuropeptides, such as alpha-melanocyte-stimulating hormone, and downregulating appetite-stimulating factors, primarily neuropeptide Y. In animal research reduced levels of leptin were associated with elevated levels of endocannabinoids in the hypothalamus, and application of leptin reduced endocannabinoid levels (Di Marzo et al. 2001). Cannabinoid induced eating is ascribed to an increase of the incentive value of food (Williams and Kirkham 2002).

Bones. Preliminary observations show that endocannabinoids seem to stimulate bone formation (Mechoulam et al. 2003). Reverse transcription polymerase chain reaction of differentiating osteoblastic precursor cells demonstrated progressive increase in mRNA levels of CB_2 but not of CB_1. In addition, normal mice treated systematically with 2-AG showed a dose dependent increase in trabecular bone formation (Mechoulam et al. 2003). The peptide leptin is known to negatively regulate both osteoblastic and endocannabinoid activity (Di Marzo et al 2001).

Digestive tract. Cannabinoid agonists inhibit gastrointestinal motility and gastric emptying in rats (Shook and Burks 1989). In a study with humans, THC caused a significant delay in gastric emptying (McCallum et al. 1999). In addition, CB agonists inhibited pentagastrin-induced gastric acid secretion in the rat (Coruzzi et al. 1999), mediated by sup-

pression of vagal drive to the stomach through activation of CB_1 receptors (Adami et al. 2002).

Eye. The evidence of cannabinoid receptors at different sites (anterior eye, retina, corneal epithelium) suggests that cannabinoids influence different physiological functions in the human eye (Pate 2002). Vasodilation in the eye is observed as conjunctival reddening after THC exposure (Dewey 1986). THC and some other cannabinoids decrease intraocular pressure (Colasanti 1990, Pate 2002). CB_1 receptors in the eye are involved in this effect while CB_2 receptor agonists do not reduce intraocular pressure (Laine et al. 2003).

Genetic and cell metabolism. THC can inhibit DNA, RNA, and protein synthesis, and can influence the cell cycle. However, very high doses are required to produce this effect *in vitro* (Tahir et al. 1992). Cannabinoid agonists inhibited human breast cancer cell proliferation *in vitro* (De Petrocellis et al. 1998, Melck et al. 2000), and, directly applied at the tumor site, showed antineoplastic activity against malignant gliomas in rats (Galve-Roperh et al. 2000).

Hormonal system and fertility. THC interacts with the hypothalamic-pituitary adrenal axis influencing numerous hormonal processes (Murphy 2002). Minor changes in human hormone levels due to acute cannabis or THC ingestion usually remain in the normal range (Hollister 1986). Tolerance develops to these effects, however, and even regular cannabis users demonstrate normal hormone levels.

Immune system. Animal and cell experiments have demonstrated that THC exerts complex effects on cellular and humoral immunity (Cabral 2002, Melamede 2002). It is not clear whether and to what extent these effects are of clinical relevance in humans with respect to beneficial inflammation (Evans et al. 1987, Sofia et al. 1973), allergies (Jan et al. 2003), autoimmune processes (Melamede 2002) and undesirable effects (decreased resistance towards pathogens and carcinogens) (Cabral 2002). THC was shown to modulate the immune response of T lymphocytes (Yuan et al. 2002). It suppressed the proliferation of T cells and changed the balance of T helper 1 (Th1) and T helper 2 (Th2) cytokines. It decreased the pro-inflammatory Th1 reaction (e.g., the production of interferon-gamma) and increased the Th2 reaction. This may explain why THC is effective against inflammation with a strong Th1 reaction, e.g., in multiple sclerosis, Crohn's disease and arthritis. The regulation of the activation and balance of human Th1/Th2 cells seems to be mediated by a CB_2 receptor-dependent pathway (Yuan et al. 2003).

Sperm. After several weeks of daily smoking 8-10 cannabis cigarettes, a slight decrease in sperm count was observed in humans, with-

out impairment of their function (Hembree et al. 1978). In animal studies high doses of cannabinoids inhibited the acrosome reaction (Chang et al. 1993).

PHARMACOLOGICAL ACTIVITY OF THC METABOLITES

11-Hydroxy-Δ^9-THC

The most important psychotropic metabolite of Δ^9-THC is 11-OH-Δ^9-tetrahydrocannabinol (11-OH-THC) (Figure 6), with a similar spectrum of actions and similar kinetic profiles as the parent molecule (Lemberger et al. 1972, Perez-Reyes et al. 1972). After intravenous administration in humans, 11-OH-THC was equipotent to THC in causing psychic effects and reduction in intraocular pressure (Perez-Reyes et al. 1972). In some pharmacological animal tests, 11-OH-THC was 3 to 7 times more potent than THC (Karler and Turkanis 1987).

11-Nor-9-Carboxy-Δ^9-THC

The most important non-psychotropic metabolite of Δ^9-THC is 11-nor-9-carboxy-THC (THC-COOH) (Figure 7). It possesses anti-inflammatory and analgesic properties by mechanisms similar to non-steroidal anti-inflammatory drugs (Burstein et al. 1989, Burstein 1999, Doyle et al. 1990). THC-COOH antagonizes some effects of the parent drug through an unknown mechanism, e.g., the cataleptic effect in mice (Burstein et al. 1987). Ajulemic acid (CT-3), a synthetic derivative of THC-COOH, shows a similar pharmacological profile as the natural substance. Recently, a possible mechanism of action was proposed for this derivative (Liu et al. 2003). Ajulemic acid bounds directly and specifically to the peroxisome proliferator-activated receptor gamma (PPAR gamma), a pharmacologically important member of the nuclear receptor

FIGURE 6. 11-OH-THC (11-hydroxy-Δ^9-THC).

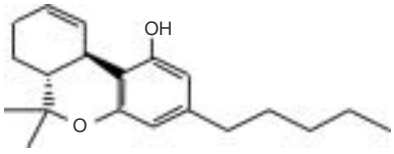
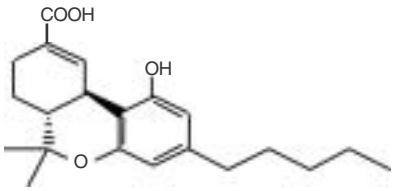


FIGURE 7. THC-COOH (11-nor-9-carboxy-Δ^9-THC).



superfamily. In addition, it was shown that ajulemic acid inhibited interleukin-8 promoter activity in a PPAR gamma-dependent manner, suggesting a link between the anti-inflammatory action of the cannabinoid acid and the activation of PPAR gamma.

PHARMACOLOGICAL EFFECTS OF OTHER CANNABINOIDS

Phytocannabinoids

Cannabidiol (CBD) is a non-psychotropic cannabinoid, for which sedating (Zuardi et al. 2002), anti-epileptic (Karler and Turkanis 1981), anti-dystonic (Consroe et al. 1986), anti-emetic (Parker et al. 2002), and anti-inflammatory (Malfait et al. 2000) effects have been observed. It reduced intraocular pressure (Colasanti et al. 1984), was neuroprotective (Hampson 2002), and antagonized the psychotropic and several other effects of THC (Zuardi et al. 1982). Anxiolytic and anti-psychotic properties might prove useful in psychiatry (Zuardi et al. 1982, Zuardi et al. 2002).

The non-psychotropic cannabinoids cannabigerol (CBG) and cannabichromene (CBC) showed sedative effects. CBG has been observed to decrease intraocular pressure (Colasanti 1990), showed antitumor activity against human cancer cells (Baek et al. 1998) and has antibiotic properties.

Endocannabinoids

Anandamide (arachidonylethanolamide), an endocannabinoid, produces pharmacological effects similar to those of THC. However, there are apparently some significant differences to THC. Under certain circumstances, anandamide acts as a partial agonist at the CB_1 receptor (Fride et al. 1995), and very low doses of anandamide antagonized the actions of THC. It is assumed that low doses of anandamide activated stimulating G_s protein pathways and not inhibiting G_i proteins, or

caused an allosteric modulation of the cannabinoid receptor (Fride et al. 1995).

Classical Synthetic Cannabinoids

Among the classical synthetic cannabinoids that retain the phytocannabinoid ring structures and their oxygen atoms are nabilone (Figure 8), HU-210, and HU-211 (Figure 9). Nabilone is available on prescription in several countries with a similar pharmacological profile as THC (Archer et al. 1986). HU-210, an analogue of Δ^8-THC with a dimethylheptyl side chain, is between 80 and 800 times more active than THC (Little et al. 1989, Ottani and Giuliani 2001), while its enantiomer (mirror image) HU-211 is completely devoid of psychoactivity (Titishov et al. 1989). The latter, also called dexanabinol, is an NMDA antagonist with neuroprotective properties in hypoxia and ischemia (Mechoulam and Shohami 2002). It is under clinical investigation for the treatment of brain injuries and stroke (Mechoulam and Shohami 2002). CT-3 or ajulemic acid (Figure 10), a derivative of the Δ^8-THC metabolite THC-COOH, is under clinical investigation for the treatment of inflammation and pain (Burstein 2002, Perez-Reyes et al. 1976).

FIGURE 8. Nabilone.

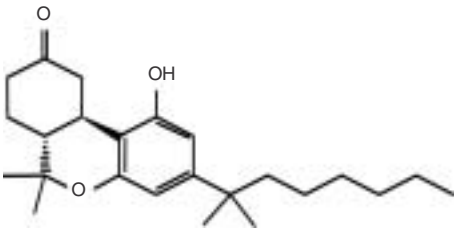


FIGURE 9. Dexanabinol (HU211).

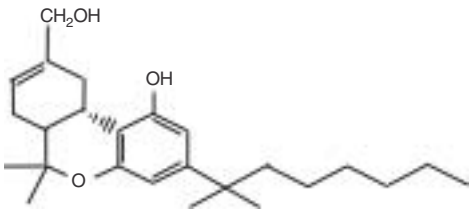
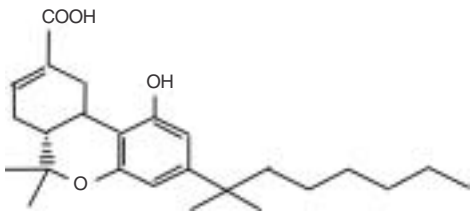


FIGURE 10. CT-3 (ajulemic acid).



Non-Classical Synthetic Cannabinoids

Levonantradol, from Pfizer, under clinical investigation for the treatment of pain (Jain et al. 1981) and the side effects of chemotherapy (Citron et al. 1985) and radiotherapy (Lucraft and Palmer 1982), is a non-classical cannabinoid with a more radical deviation of the typical structure. Other non-classical cannabinoids are the aminoalkylindol WIN-55,212-2, which has a 6.75-fold selective affinity towards the CB_2 receptor (Showalter et al. 1996) and the bicyclic cannabinoid analogue CP-55,940, a widely-used agonist for the testing of cannabinoid receptor affinity, with potency 4-25 times greater than THC, depending on assay (Melvin et al. 1993).

Anandamide Analogues

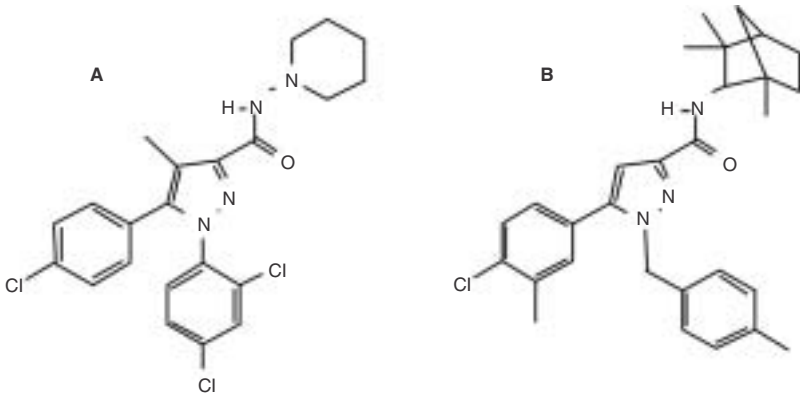
Several anandamide congeners have been synthesized (Abadji et al. 1994), among them (*R*)-(+)-α-methanandamide that possesses both a four-fold higher affinity for the CB_1 receptor and a greater catabolic resistance than anandamide. Fatty acid-based compounds have been synthesized that mimic the structure of anandamide, but act as inhibitors of the catabolic amidase enzyme, the "fatty acid amide hydrolase" (FAAH) (Di Marzo 1998).

AM-404 is a synthetic fatty amide that acts as a selective inhibitor of anandamide transport, thus preventing cellular re-uptake of anandamide (Beltramo et al. 1997) and increasing circulating anandamide levels (Giuffrida et al. 2001).

Therapeutic Potential of Antagonists

SR141716A (Figure 11) has been shown to improve memory in rodents (Terranova et al. 1996) and cause hyperalgesia (Jaggar et al. 1998). This

FIGURE 11. Cannabinoid receptor antagonists, SR 141716A (A), a selective CB_1 receptor antagonist, and SR 144528 (B), a selective CB_2 receptor antagonist.



antagonist was also able to block the psychological and physiological effects of THC in humans in a dose-dependent manner (Huestis 2001). A possible therapeutic potential was proposed for obesity (Huestis et al. 2001), schizophrenia (Huestis et al. 2001), in conditions with lowered blood pressure, e.g., liver cirrhosis (Wagner et al. 2001), Parkinson's disease (Di Marzo et al. 2000b), Huntington's disease (Müller-Vahl et al. 1999), alcohol dependency (Vacca et al. 2002, Racz et al. 2003) and to improve memory in Alzheimer's disease (Huestis et al. 2001).

TOLERANCE AND DEPENDENCY

Tolerance

Tolerance develops to most of the THC effects (Romero et al. 1997), among them the cardiovascular, psychological and skin hypothermic effects (Jones et al. 1976, Stefanis 1978), analgesia (Bass and Martin 2000), immunosuppression (Luthra et al. 1980), corticosteroid release (Miczek and Dixit 1980), and disruption of the hypothalamo-hypophyseal axis (Smith et al. 1983), causing alterations in endocannabinoid formation and contents in the brain (Di Marzo et al. 2000). In a 30-day study, volunteers received daily doses of 210 mg oral THC and developed tolerance to cognitive and psychomotor impairment and to the

psychological high by the end of the study (Jones and Benowitz 1979). After a few days an increased heart rate was replaced by a normal or a slowed heart rate. Tolerance develops also to orthostatic hypotension (Benowitz and Jones 1975).

Tolerance can mainly be attributed to pharmacodynamic changes, presumably based on receptor downregulation and/or receptor desensitisation (Di Marzo et al. 2000, Rubino et al. 2000b). Rate and duration of tolerance varies with different effects. Rats receiving THC over a period of five days exhibited a decreased specific binding ranging from 20 to 60% in different receptor sites of the brain compared to controls (Romero et al. 1997). However, in another study no significant alteration in receptor binding was observed after chronic administration of THC resulting in a twenty-sevenfold behavioral tolerance (Abood et al. 1993). Chronic administration of anandamide as well resulted in behavioral tolerance without receptor downregulation (Rubino et al. 2000a), and it was proposed that desensitization of the CB_1 receptor might account for this observation (Rubino et al. 2000a). Tolerance has been observed to occur together with modified biotransformation activities with regard to mitochondrial oxygen consumption, monooxygenase activities, and the content of liver microsomal cytochrome P450 (Costa et al. 1996). However, only a small proportion of tolerance can be attributed to changes in metabolism (Hunt and Jones 1980).

Withdrawal and Dependency

After abrupt cessation of chronic dosing with high doses of THC, withdrawal has been observed in humans (Georgotas and Zeidenberg 1979, Jones and Benowitz 1976). Subjects complained of inner unrest, irritability, and insomnia and presented "hot flashes," sweating, rhinorrhea, loose stools, hiccups, and anorexia. Withdrawal symptoms in humans are usually mild and the risk for physical and psychic dependency is low compared to opiates, tobacco, alcohol, and benzodiazepines (Anthony et al. 1994, Kleiber et al. 1997, Roques 1998). A review of several indicators of the abuse potential of oral dronabinol in a therapeutic context found little evidence of such a problem (Calhoun et al. 1998).

THERAPEUTIC USES

Cannabis preparations have been employed in the treatment of numerous diseases, with marked differences in the available supporting

data (British Medical Association 1997, Grotenhermen and Russo 2002, House of Lords 1998, Joy et al. 1999). Besides phytocannabinoids, several synthetic cannabinoid derivatives are under clinical investigation that are devoid of psychotropic effects, and modulators of the endocannabinoid system (re-uptake inhibitors, antagonists at the CB receptor, etc.) will presumably follow.

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 crude cannabis products (usually without legal sanction). The anti-emetic (Dansak 1997), and the appetite enhancing effects (Plasse et al. 1991), muscle relaxation (Clifford 1983), analgesia (Noyes and Baram 1974), and therapeutic use in Tourette's syndrome (Müller-Vahl et al. 1997) were all discovered or re-discovered in this manner.

Incidental observations have also revealed therapeutically useful effects. This occurred in a study of Volicer et al. (1997) in patients with Alzheimer's disease wherein 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 drug. The discovery of decreased intraocular pressure with THC administration in the beginning of the 1970s was also serendipitous (Hepler and Frank 1971), when several research groups screened for effects of marijuana on the human body.

HIERARCHY OF THERAPEUTIC EFFECTS

Possible indications for cannabis preparations have been extensively reviewed (British Medical Association 1997, Grinspoon and Bakalar 1993, Grotenhermen and Russo 2002, Grotenhermen 2002a, House of Lords 1998, Joy et al. 1999, Mathre 1997, Mechoulam 1986). To do justice to the scientific evidence with regard to different indications, a hierarchy of therapeutic effects can be devised, with established, relatively well-confirmed, less confirmed and effects at a basic research stage. However, the history of research into the therapeutic benefits of cannabis and cannabinoids has demonstrated that the scientific evidence for a specific indication does not necessarily reflect the actual therapeutic potential for a given disease, but sometimes obstacles to clinical research.

Established Effects

Marinol™ (dronabinol, Δ^9-THC) is approved for medical use in refractory nausea and vomiting caused by antineoplastic drugs used for the treatment of cancer (Abrahamov et al. 1995, Dansak 1997, Lane et al. 1991, Sallan et al. 1980) and for appetite loss in anorexia and cachexia of HIV/AIDS patients (Beal et al. 1995, Beal et al. 1997, Plasse et al. 1991). These effects can be regarded as established effects for THC and cannabis. THC is also effective in cancer cachexia (Jatoi et al. 2002) and nausea induced by syrup of ipecac (Soderpalm et al. 2001). Cesamet™ (nabilone) is approved for nausea and vomiting associated with cancer chemotherapy.

Relatively Well-Confirmed Effects

Spasticity due to spinal cord injury (Brenneisen et al. 1996, Maurer et al. 1990, Petro 1980), multiple sclerosis (Brenneisen et al. 1996, Killestein et al. 2002, Martyn et al. 1995, Meinck et al. 1989, Petro 1980, Petro and Ellenberger 1981, Ungerleider et al. 1987), and other reasons (Lorenz 2002), chronic painful conditions, especially neurogenic pain (Elsner et al. 2001, Holdcroft et al. 1997, Maurer et al. 1990, Notcutt et al. 2001a, Notcutt et al. 2001b, Noyes et al. 1975a, Noyes et al. 1975b, Petro 1980, Wade et al. 2003), movement disorders (including Tourette's syndrome, dystonia and levodopa-induced dyskinesia) (Clifford 1983, Fox et al. 2002, Hemming and Yellowlees 1993, Müller-Vahl et al. 1999, Müller-Vahl et al. 2002, Müller-Vahl et al. 2003, Sandyk and Awerbuch 1998, Sieradzan et al. 2001), asthma (Hartley et al. 1978, Tashkin et al. 1974, Williams et al. 1976) and glaucoma (Crawford and Merritt 1979, Hepler and Frank 1971, Hepler and Petrus 1976, Merritt et al. 1980, Merritt et al. 1981) can be regarded as relatively well-confirmed effects with small placebo controlled trials demonstrating benefits. However, results were sometimes conflicting. In contrast to other studies, Clermont-Gnamien et al. (2002) did not find any therapeutic effect of oral dronabinol titrated to the maximum dose of 25 mg/day (mean dose: 15 ± 6 mg), during an average of 55 days in seven patients with chronic refractory neuropathic pain. Killestein et al. (2002) were unable to find any benefits of THC and capsulated cannabis extract in MS patients with severe spasticity but doses applied (2×2.5 mg or 2×5 mg THC) were probably too low to get the desired therapeutic effects.

Less Confirmed Effects

There are several indications in which mainly case reports suggest benefits. These are allergies (Schnelle et al. 1999), inflammation (Joy et al. 1999), epilepsy (Gordon and Devinsky 2001), intractable hiccups (Gilson and Busalacchi 1998), depression (Beal et al. 1995), bipolar disorders (Grinspoon and Bakalar 1998), anxiety disorders (Joy et al. 1999), dependency to opiates and alcohol (Mikuriya 1970, Schnelle et al. 1999), withdrawal symptoms (Mikuriya 1970), and disturbed behavior in Alzheimer's disease (Volicer et al. 1997).

BASIC RESEARCH STAGE

Basic research shows promising possible future therapeutic uses, among them neuroprotection in hypoxia and ischemia due to traumatic head injury, nerve gas damage and stroke (Hampson 2002, Mechoulam and Shohami 2002). Some immunological mechanisms of THC hint to possible benefits in autoimmune diseases, such as multiple sclerosis, arthritis, and Crohn's disease (Melamede 2002). In a murine model of multiple sclerosis, cannabinoids significantly improved the neurological deficits in a long-lasting way. On a histological level they reduced microglial activation and decreased the number of CD4+ infiltrating T cells in the spinal cord (Arevalo-Martin et al. 2003). Another group found that amelioration of clinical disease in the same MS model was associated with downregulation of myelin epitope-specific Th1 effector functions (delayed-type hypersensitivity and IFN-gamma production) and the inhibition of the proinflammatory cytokines, TNF-alpha, interleukin 1-beta, and interleukin-6 (Croxford and Miller 2003). Several phytocannabinoids possess an anti-allergic potential. THC and cannabinol attenuated the increase of the interleukins IL-2, IL-4, IL-5, and IL-13 in reaction to sensitization with ovalbumin in mice. In addition, the elevation of serum IgE and the mucus overproduction induced by ovalbumin was markedly attenuated by the two cannabinoids (Jan et al. 2003).

Anti-neoplastic activity of THC came into the focus of research after a long-term animal study, designed to investigate THC's potential carcinogenicity, resulted in better survival of rats dosed with THC than controls due to lower incidence for several types of cancer (Chan et al. 1996). Frequency of testicular interstitial cell, pancreas and pituitary gland adenomas in male rats, mammary gland fibroadenoma and uterus stromal polyp in female rats was reduced in a dose-related manner.

Later studies showed that cannabinoids exerted antineoplastic activity in malignant gliomas (Jacobsson et al. 2001, Sanchez et al. 2001) and malignant skin tumors (Casanova et al. 2003). CB1 and CB2 receptor agonists were both effective. Cannabinoids seem to be able to control the cell survival/death decision (Guzman et al. 2001). Thus, cannabinoids may induce proliferation, growth arrest, or apoptosis in a number of cells depending on dose (Guzman et al. 2001). Cannabinoids were also shown to inhibit angiogenesis of malignant gliomas by at least two mechanisms, direct inhibition of vascular endothelial cell migration and survival as well as the decrease of the expression of proangiogenic factors (Blazquez et al. 2003). A first human Phase I-II trial to investigate the tolerability and efficacy of intracranially applied THC (dronabinol) in glioblastoma multiforme is under way in Spain.

Other fields of research are disorders of circulation and blood pressure (Ralevic and Kendall 2001, Wagner et al. 2001). In rats, daily application of a CB_1 agonist after experimental infarction prevented signs of heart failure, endothelial dysfunction and hypotension; however, the cannabinoid also increased left-ventricular end-diastolic pressure, which may be negative in the long run (Wagner et al. 2003).

Several effects observed in animal studies provide the basis for further research, among them effects against diarrhea in mice (Izzo et al. 2000), inhibition of bronchospasm provoked by chemical irritants in rats (Calignano et al. 2000), and stabilization of respiration in sleep-related breathing disorders (e.g., apnea) (Carley et al. 2002).

Some effects that are usually regarded as side effects may be also of advantage in certain pathological situations, among them the disturbance of short-term memory. Patients suffering from posttraumatic stress disorders want to forget and there are anecdotal reports on their benefits from cannabis (Gieringer 2002). Animal research has demonstrated that CB_1-deficient mice showed strongly impaired short-term and long-term extinction of aversive memories (Marsicano et al. 2002), which may explain some of the anxiety reducing effects in posttraumatic stress disorder and similar conditions (Sah 2002).

DRUG INTERACTIONS

Interactions with other drugs may depend on activity on similar effector systems or metabolic interactions (Pryor et al. 1976). Since cannabinoids are strongly bound to proteins, interactions with other protein bound drugs may also occur. They might also interact with

drugs that, such as THC, are metabolized by enzymes of the cytochrome P-450 complex. However, there was only a minor influence of cannabis smoking and oral dronabinol on pharmacokinetic parameters of antiretroviral medication used in HIV infection and metabolized by cytochrome P-450 enzymes, and the use of cannabinoids was regarded as unlikely to impair antiretroviral efficacy (Kosel et al. 2002). Tobacco and cannabis smoking cessation was reported to result in elevated blood levels of antipsychotic medication (clozapine or olanzapine), due to cessation of induction of cytochrome $P450_{1A2}$ (CYP1A2) by smoke constituents (Zullino et al. 2002).

Other medicines may enhance or attenuate certain actions of THC or certain actions of these medicines may be enhanced or attenuated by THC (Hollister 1999, Sutin and Nahas 1999). 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. In a study by Lane et al. (1991), a combination of prochlorperazine and dronabinol was more effective in reducing unwanted effects of the antineoplastic medication than the phenothiazine alone and the incidence of cannabinoid-induced adverse effects was decreased when dronabinol was combined with prochlorperazine, which also has antipsychotic properties. Cannabis, caffeine and tobacco reduced the blood pressure reactivity protection of ascorbic acid, probably through their dopaminergic effects (Brody and Preut 2002).

Of greatest clinical relevance is reinforcement of the sedating effects of other psychotropic substances (alcohol, benzodiazepines), and the interaction with substances that act on heart and circulation (amphetamines, adrenaline, atropine, beta-blockers, diuretics, tricyclic antidepressants, etc.) (Hollister 1999, Sutin and Nahas 1999).

A number of additive effects may be desirable, such as the enhancement of muscle relaxants, bronchodilators and anti-glaucoma medication (Pate 2002), of analgesia by opiates (Welch and Eads 1999, Cichewicz and McCarthy 2003), the antiemetic effect of phenothiazines (Lane et al. 1991), and the antiepileptic action of benzodiazepines (Koe et al. 1985). THC may antagonize the antipsychotic actions of neuroleptics (Sutin and Nahas 1999) and may improve their clinical responsiveness in motor disorders (Moss et al. 1989). A combination with other drugs may be desirable not only to reduce side effects of the single drugs but also to prevent the development of tolerance. In animal studies, tolerance to morphine was reduced by simultaneous administration of THC (Cichewicz and Welch 2003). Chronic treatment with high doses of oral morphine produced a threefold tolerance of pain-reducing effects. Tol-

erance to morphine was prevented in groups receiving a daily co-treatment with low doses of THC (Cichewicz and Welch 2003).

Since the endocannabinoid system is linked with hormonal control there may be interactions in this area. The progesterone receptor inhibitor mifepristone, which is approved for the termination of early pregnancy, and the glucocorticoid synthesis inhibitor metyrapone was recently shown to potentiate the sedating effects of high THC doses in mice (Pryce et al. 2003).

The cyclooxygenase inhibitors indomethacin, acetylsalicylic acid, and other non-steroidal anti-inflammatory drugs antagonize THC effects. Indomethacin significantly reduced subjective "high" (Perez-Reyes et al. 1991), tachycardia (Perez-Reyes et al. 1991), decrease of contractile performance in heart muscle (Bonz et al. 2003) and decrease of intraocular pressure following topical THC (eye drops) (Green et al. 2001), reflecting the involvement of cyclooxygenase activity in several THC effects.

CONCLUSIONS

The discovery, within the past 15 years, of a system of specific cannabinoid receptors in humans and their endogenous ligands has strongly stimulated research with about 800 articles published in Medline listed journals in 2002, compared to about 250 twenty years ago. It becomes apparent that the endocannabinoid system is playing a major role in signal transduction in neuronal cells, and arachidonylethanolamide (anandamide) seems to be a central inhibitory compound in the central nervous system (Mechoulam et al. 1998).

Mechanisms of action of cannabinoids are complex, not only involving activation of and interaction at the cannabinoid receptor, but also activation of vanilloid receptors (Jacobsson et al. 2001), influence of endocannabinoid concentration (Bisogno et al. 2001), antioxidant activity (Hampson 2002), metabolic interaction with other compounds, and several others. There is still much to learn about the physiological role of the natural ligands to the CB receptors and about long-term effects of cannabis use. However, due to the millennia-long use of cannabis for recreational, religious and medicinal purposes, which in recent decades was accompanied by scientific investigation in several disciplines, we do not expect to encounter with the medicinal use of cannabinoids the same unpleasant surprises that occasionally occur with newly designed synthetic drugs.

Many people who suffer from severe illnesses have discovered cannabis as a beneficial remedy, and public opinion surveys in Europe and North America show that increasing numbers of citizens reject criminal prosecution of patients who benefit from the drug. The psychotropic and circulatory effects of CB_1 receptor agonists and the stigma of cannabis as a recreational and addicting drug are still major obstacles to the legal therapeutic utilization of the whole range of potentially beneficial effects. Properly designed and executed clinical studies are necessary to verify anecdotal experiences and the results from smaller uncontrolled studies, and to overcome uncertainties and skepticism.

Aside from phytocannabinoids and cannabis preparations, cannabinoid analogues that do not bind to the CB_1 receptor are attractive compounds for clinical research, among them dexanabinol and CT-3. Additional ideas for the separation of the desired therapeutic effects from the psychotropic action comprise the concurrent administration of THC and CBD, the design of CB_1 receptor agonists that do not cross the blood brain barrier, and the development of compounds that influence endocannabinoid levels by inhibition of their membrane transport (transport inhibitors) or hydrolysis (FAAH inhibitors). For example, blockers of anandamide hydrolysis were able to reduce anxiety in animal tests (Kathuria et al. 2003). These benzodiazepine-like properties were accompanied by augmented brain levels of anandamide and were prevented by CB_1 receptor blockade. It is remarkable that FAAH inhibitors may already be in clinical use as proposed by Fowler (2003). The non-steroidal anti-inflammatory agent fluriprofen inhibits the metabolism of FAAH and intrathecally administrated fluriprofen reduced inflammatory pain by a mechanism that was blocked by a CB_1 receptor antagonist (Fowler 2003).

The future will show which drugs that target the endogenous cannabinoid system will follow dronabinol and nabilone into the pharmacy and which indications will prove successful in clinical trials.

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