

Pharmacology of Cannabinoids

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Abstract

Dronabinol (Δ^9 -tetrahydrocannabinol, THC), the main source of the pharmacological effects caused by the use of cannabis, is an agonist to both the CB₁ and the CB₂ subtype of cannabinoid receptors. It is available on prescription in several countries. The non-psychotropic cannabidiol (CBD), some analogues of natural cannabinoids and their metabolites, 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 including spleen, leukocytes; reproductive, urinary and gastrointestinal tracts; endocrine glands, arteries and heart.

Five endogenous cannabinoids have been detected so far, of whom anandamide and 2-arachidonylglycerol are best characterized. 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 the cannabinoid system that include motor coordination, memory procession, control of appetite, 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.

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.

Introduction

In the 1930s and 1940s the chemical structure of the first phytocannabinoids had been successfully characterized [1]. However, it was not until 1964 that Δ^9 -tetrahydrocannabinol (Δ^9 -THC, dronabinol), mainly responsible for the pharmacological effects of the cannabis plant [2, 3], was stereochemically defined, and synthesized. Another scientific breakthrough in cannabinoid research was the detection of a system of specific cannabinoid receptors in mammals and their endogenous ligands which constitute the cannabinoid system, within the past 15 years.

About 65 cannabinoids have been detected in the cannabis plant [4], of whom cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), Δ^9 -THC, and cannabinol (CBN) are the most relevant in quantity. The THC main effects may be modulated by other cannabinoids, mainly CBD, and other cannabis constituents [5]. 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 potential therapeutic uses.

In a medical context Δ^9 -THC is usually called dronabinol. Synthetic dronabinol is available on prescription in the US, Canada and several other countries as MarinolTM. In Germany two firms produce dronabinol for medical uses semi-synthetically from fiber hemp by extraction of cannabidiol and isomerization to dronabinol. Since 2003 two government approved qualities of cannabis are available in Dutch pharmacies with a dronabinol content of 13% and 18%, respectively.

Mechanism of Action

The mechanism of action of cannabinoids is best investigated for Δ^9 -THC (THC, dronabinol) 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.

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 [6], some neuroprotective effects [7], and anti-emetic effects. 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.

The mode of action of cannabidiol is not fully understood and several mechanisms have been proposed:

- (1) CBD acts as antagonist at the central CB₁ receptor and was able to inhibit several CB₁ mediated THC effects [8]. In a study by Petitet et al. (1998), CBD considerably reduced the receptor activation of a potent classical CB₁ receptor agonist.
- (2) CBD stimulates the vanilloid receptor type 1 (VR₁) with a maximum effect similar in efficacy to that of capsaicin [9, 10].

- (3) CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration [9, 11].
- (4) Finally, CBD may also increase the plasma THC level [12] by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system [13, 14]. However, there was no or minimal effect of CBD on plasma levels of THC in man [15, 16].

Cannabinoid Receptors

To date two cannabinoid receptors have been identified, the CB₁ (cloned in 1990), and the CB₂ receptor (cloned in 1993) [17], 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 [18]. Activation of cannabinoid receptors causes inhibition of adenylate cyclase, thus, inhibiting the conversion of ATP to cyclic AMP (cAMP). Other effects have also been observed, e.g. interaction with certain ion channels.

CB₁ receptors are mainly found on neurones 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 [17]. CB₁ 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 [18], which may account for the lack of cannabis-related acute fatalities, e.g. due to depression of respiration.

CB₂ receptors are located principally in immune cells, among them leukocytes, spleen and tonsils [19]. Immune cells also express CB₁ receptors but there is markedly more mRNA for CB₂ than CB₁ receptors in the immune system. One of the functions of CB receptors in the immune system is modulation of cytokine release. Activation of the CB₁ receptor produces marijuana-like effects on psyche and circulation, while activation of the CB₂ receptor does not. Hence, selective CB₂ receptor agonists have become an increasingly investigated target for therapeutic uses of cannabinoids, among them analgesic, anti-inflammatory and anti-neoplastic actions [20, 21].

There is increasing evidence for the existence of additional cannabinoid receptor subtypes in the brain and periphery [22, 23, 24, 25].

Endocannabinoids

The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, called endocannabinoids, a family of eicosanoids [26, 27, 28]. To date five endocannabinoids have been identified. These are *N*-arachidonyl ethanolamide (anandamide) [26], 2-arachidonylglycerol (2-AG)

[29, 28], 2-arachidonylglyceryl ether (noladin ether) [30], *O*-arachidonyl-ethanolamine (virodhamine) [31], and *N*-arachidonyl-dopamine (NADA) [32].

Cannabinoid receptors and their endogenous ligands together constitute the cannabinoid system which is teleologically millions of years old and has been found in mammals and many other species [33]. Endocannabinoids serve as neurotransmitters or neuromodulators [18]. Anandamide and NADA do not only bind to cannabinoid receptors but also stimulate vanilloid receptors (VR₁) [34, 32], non-selective ion channels associated with hyperalgesia.

The first two discovered endocannabinoids, anandamide and 2-AG, are best studied. They are produced "on demand" by cleavage of membrane lipid precursors and released from cells in a stimulus-dependent manner [27]. 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) [35, 27] and other metabolic processes, including hydrolysis of 2-AG by monoglyceride lipase [36].

Tonic Activity of the Endocannabinoid System

When administered by themselves antagonists at the cannabinoid receptor may behave as inverse agonists in several bioassay systems. This means that they do not only block the effects of endocannabinoids but produce effects that are opposite in direction from those produced by cannabinoid receptor agonists, e.g. cause hyperalgesia [37], suggesting that the cannabinoid system is tonically active. This tonic activity may be due to a constant release of endocannabinoids or from the result of a portion of cannabinoid receptors which exist in a constitutively active state [19].

Tonic activity of the cannabinoid system has been demonstrated in several conditions. Elevated levels of endocannabinoid have been demonstrated in a pain circuit of the brain (periaqueductal gray) following painful stimuli [38]. 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 [39]. An increase of cannabinoid receptors following nerve damage was demonstrated in a rat model of chronic neuropathic pain [40] and in a mice model of intestinal inflammation [41]. 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 [42] and with regard to vomiting in emetic circuits of the brain [43].

Pharmacological Effects of THC

The activation of the cannabinoid system through THC and other phytocannabinoids, synthetic cannabinoids and endocannabinoids causes numerous actions, that have been extensively reviewed [44, 2, 45, 46, 3, 47, 48, 49]. Additional non-receptor mediated ef-

fects have come into focus as well [7]. 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 [50].

Toxicity

The median lethal dose (LD₅₀) of oral THC in rats was 800–1900 mg/kg depending on sex and strain [51]. 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) [51]. Acute fatal cases in humans have not been substantiated. However, myocardial infarction may be triggered by THC due to effects on circulation [52, 53]. This is unlikely to happen in healthy subjects but in persons with coronary heart disease for whom orthostatic hypotension or increased heart rate may pose a risk.

Adverse effects of medical cannabis use are within the range of effects tolerated for other medications [47, 48]. It is controversial whether heavy regular consumption may result in longterm impairment of cognition [54, 55, 56], but irreversible impairment seems to be minimal if it exists [54, 57]. 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 [58]. 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 [58].

Long-term medical use of cannabis for more than 15 years has been reported to be well-tolerated without significant physical or cognitive impairment [59]. There is conflicting evidence that infants exposed to THC *in utero* suffer developmental and cognitive impairment [60]. Marijuana can induce a schizophrenic psychosis in vulnerable persons [46, 61] and there is increasing evidence that there is a distinct cannabis psychosis [62].

Psyche, Cognition and Behavior

In humans THC or cannabis consumption, respectively, 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 [63]. It may induce sleep [64, 65]. Acute THC intoxication impairs learning and memory [66, 67, 68], and adversely affects psychomotor and cognitive performance [61], reducing the ability to drive a car and to operate machinery.

Psychological effects of THC 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) [69].

Central Nervous System and Neurochemistry

Cannabinoids interact with a multitude of neurotransmitters and neuromodulators [2, 70, 71], among them acetylcholine, dopamine, γ -aminobutyric acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and opioid peptides (see Table 1). 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 [72, 63] are mediated by effects of THC on release and turn-over of acetylcholine [72]. In a rat model cannabinoid agonists inhibited the activation of 5-HT₃ receptors. This may explain antiemetic properties of cannabinoids to be based on interactions with serotonin [73]. Therapeutic effects in movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutamergic and dopaminergic transmitters systems [74, 75].

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. 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 [76] and blocked other effects related to behavioral effects of CB₁ agonists [77, 78], in humans opioid receptor antagonists did not block the subjective effects of THC in one study [79] or even increased the subjective effects THC in another study [80].

One important physiological role of endocannabinoids is neuroprotection [81]. Ischemia and hypoxia in the CNS induce abnormal glutamate hyperactivity and other processes that cause neuronal damage. These processes play also a role in chronic neurodegenerative diseases such as Parkinson's and Alzheimer's disease and multiple sclerosis. Neuroprotective cannabinoid mechanisms observed in animal studies include 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 [82, 7, 81]. 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 [83]. Clinical studies under way investigating the therapeutic potential of a non-psychotropic derivative of THC in acute conditions (head trauma) showed first positive results [84].

Circulatory System

THC can induce tachycardia [85] and increase cardiac output with increased cardiac labor and oxygen demand [86]. It can also produce peripheral vasodilation and orthostatic hypotension [87, 3].

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) [88], which can be attenuated by beta-blockers [85]. Regular use can lead to bradycardia [87]. The cannabinoid system seems to play a major role in the control of blood pressure. Hypotension is mediated by central inhibition of the sympathetic, obviously by activation of CB₁ receptors since this effect can also be prevented by a CB₁ antagonist [89]. Endocannabinoids are produced by the vascular endothelium, circulating macrophages and platelets [90]. Vascular resistance in the coronaries and the brain is lowered primarily by direct activation of vascular cannabinoid CB₁ receptors [91].

TABLE 1. Neurotransmitter functions under cannabinoid control (modified according to: Baker et al. 2003)

Neurotransmitter	Associated disorder
<i>Excitatory amino acids</i>	
Glutamate	Epilepsy, nerve-cell death in ischemia and hypoxia (stroke, head trauma, nerve gas toxicity)
<i>Inhibitory amino acids</i>	
GABA	Spinal cord motor disorders, epilepsy, anxiety
Glycine	Startle syndromes
<i>Monoamines</i>	
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

Some Other Organ Systems and Effects

Appetite and eating. The cannabinoid system plays a critical role in milk ingestion of new-born mice [24]. Blockade of the CB₁ receptor results in death of new-borns. Endocannabinoids in the hypothalamus are part of the brain's complex system for controlling appetite which is regulated by leptin [42]. 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 and downregulating appetite-stimulating factors. In animal research, reduced levels of leptin were associated with elevated levels of endocannabinoids in the hypothalamus [42]. Cannabinoid-induced eating is ascribed to an increase of the incentive value of food [92].

Bone formation. Preliminary observations show that endocannabinoids seem to stimulate bone formation [93]. Differentiated osteoblastic precursor cells demonstrated progressive increase in mRNA levels of CB₂ receptors. In addition normal mice treated systematically with 2-AG showed a dose dependent increase in trabecular bone formation [93].

Cancer. Cannabinoid agonists inhibited human breast cancer cell proliferation *in vitro* [94, 95], and, directly applied at the tumor site, showed antineoplastic activity against malignant gliomas in rats [96].

Digestive tract. Cannabinoid agonists inhibit gastrointestinal motility and gastric emptying in rats [97]. In a study with humans THC caused a significant delay in gastric emptying [98]. In addition, CB agonists inhibited pentagastrin-induced gastric acid secretion in the rat [99].

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 [100]. Vasodilation in the eye is observed as conjunctival reddening after THC exposure [2]. THC and some other cannabinoids decrease intraocular pressure [100]. CB₁ receptors in the eye are involved in this effect while CB₂ receptor agonists do not reduce intraocular pressure [101].

Hormonal system and fertility. THC interacts with the hypothalamic-pituitary adrenal axis influencing numerous hormonal processes [102]. Minor changes in human hormone levels due to acute cannabis or THC ingestion usually remain in the normal range [3]. Tolerance develops to these effects, 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 [103, 104]. THC was shown to modulate the immune response of T lymphocytes [105]. 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 inflam-

mation with a strong Th1 reaction, e.g. in multiple sclerosis, Crohn's disease and arthritis.

Sperm. After several weeks of daily smoking 8–10 cannabis cigarettes a slight decrease in sperm count was observed in humans, without impairment of their function [106]. In animal studies high doses of cannabinoids inhibited the acrosome reaction [107].

Pharmacological Effects of Other Cannabinoids

Cannabidiol (CBD) is a non-psychotropic cannabinoid, for which sedating [108], anti-epileptic [109], anti-dystonic [110], anti-emetic [111], and anti-inflammatory [112] effects have been observed. It reduced intraocular pressure [113], was neuroprotective [7], and antagonized the psychotropic and several other effects of THC [8]. Anxiolytic and anti-psychotic properties might prove useful in psychiatry [8, 108].

Among the classical synthetic cannabinoids that retain the phytocannabinoid ring structures and their oxygen atoms are nabilone, HU-210, and HU-211. Nabilone is available on prescription in several countries with a similar pharmacological profile as THC [114]. HU-211 is completely devoid of psychoactivity. It is also called dexanabinol, an NMDA antagonist with neuroprotective properties in hypoxia and ischemia [81]. It is under clinical investigation for the treatment of brain injuries and stroke [91]. CT-3 or ajulemic acid, a derivative of the Δ⁸-THC metabolite THC-COOH, is under clinical investigation for inflammation and pain [115].

Anandamide (arachidonyl ethanolamide), 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 CB₁ receptor [116], and very low doses of anandamide antagonized the actions of THC. Anandamide also stimulates the vanilloid receptor (VR₁) [32]. 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".

Tolerance and Dependence

Tolerance develops to most of the THC effects [117], causing alterations in endocannabinoid formation and contents in the brain [118]. In a 30-day study, volunteers, who received daily doses of 210 mg oral THC, developed tolerance to cognitive and psychomotor impairment and to the psychological high by the end of the study [119]. After a few days an increased heart rate was replaced by a normal or a slowed heart rate. Tolerance develops also to orthostatic hypotension [87].

Tolerance can mainly be attributed to pharmacodynamic changes, presumably based on receptor downregulation and/or receptor desensitisation [118, 120]. Rate and duration of tolerance varies with different effects.

After abrupt cessation of chronic dosing with high doses of THC withdrawal has been observed in humans [121, 119]. 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 [122, 123, 124]. A review of several indicators of the abuse potential of oral dronabinol in a therapeutic context found little evidence of such a problem [125].

Drug Interactions

Other medicines may enhance or attenuate certain actions of THC or certain actions of these medicines may be enhanced or attenuated by 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. 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 [126].

Of the greatest clinical relevance is the 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.) [127]. A number of additive effects may be desirable, such as the enhancement of muscle relaxants, bronchodilators and anti-glaucoma medication [100], of analgesia by opiates [128], the antiemetic effect of phenothiazines [126], and the antiepileptic action of benzodiazepines [129].

The cyclooxygenase inhibitors indomethacin, acetylsalicylic acid, and other non steroidal anti-inflammatory drugs antagonize THC effects. Indomethacin significantly reduced subjective "high" [130], tachycardia [130], decrease of contractile performance in heart muscle [131] and decrease of intraocular pressure following topical THC (eye drops) [132], reflecting the involvement of cyclooxygenase activity in several THC effects.

Therapeutic Uses

Cannabis preparations have been employed in the treatment of numerous diseases. Besides phytocannabinoids, several synthetic cannabinoid derivatives are under clinical investigation that are devoid of psychotropic effects, and modulators of the endocannabinoid system (such as re-uptake inhibitors, antagonists at the CB receptor, etc.) will presumably follow.

Possible indications for cannabis preparations have been extensively reviewed [45, 47, 48, 71; 127, 133, 134, 135, 136, 137]. To do justice to the scientific evidence with regard to different indications, a hierar-

chy of therapeutic effects can be devised: 1) clinically, established, 2) clinically relatively well-confirmed, 3) clinically less confirmed and 4) preclinical evidence for the therapeutic potential available.

1. Established Effects

Marinol™ (dronabinol, Δ^9 -THC) is approved for the medical use in refractory nausea and vomiting caused by antineoplastic drugs used for the treatment of cancer and for appetite loss in anorexia and cachexia of HIV/AIDS patients. These effects can be regarded as established effects for THC and cannabis. THC is also effective in cancer cachexia and nausea induced by syrup of ipecac. Cesamet™ (nabilone) is approved for nausea and vomiting associated with cancer chemotherapy.

2. Relatively Well-Confirmed Effects

In recent years there is also increasing evidence for therapeutic effects of THC and cannabis extracts in spasticity due to multiple sclerosis and spinal cord injury, chronic pain and Tourette's syndrome. Effects in some other movement disorders (including dystonia and levodopa-induced dyskinesia), in asthma and glaucoma can also be regarded as relatively well-confirmed effects with small placebo controlled trials demonstrating benefits. However, results were sometimes conflicting.

3. Less Confirmed Effects

There are several indications, in which mainly case reports suggest benefits. These are allergies, inflammation, epilepsy, intractable hiccups, depression, bipolar disorders, anxiety disorders, dependency to opiates and alcohol, withdrawal symptoms, and disturbed behavior in Alzheimer's disease.

4. 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 [7, 81]. Initial clinical results are available for dexanabinol [84]. Some immunological mechanisms of THC hint to possible benefits in autoimmune diseases, such as multiple sclerosis, arthritis, and Crohn's disease [104]. Several phytocannabinoids possess anti-allergic potential. THC and cannabidiol 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 [138].

Anti-neoplastic activity of THC came into focus in a study designed to investigate THC's potential carcinogenicity. Surprisingly, long-term treatment of rats with THC, resulted in better survival of rats dosed with THC than controls due to lower incidence for several types of cancer [139]. Later studies showed that cannabinoids exerted antineoplastic activity in malignant gliomas [21] and malignant skin tumors [140].

Cannabinoids were also shown to inhibit angiogenesis of malignant gliomas [141].

Other fields of research are disorders of circulation and blood pressure [142, 143]. In rats daily application of a CB₁ 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 [144]. Several effects observed in animal studies provide the basis for further research, among them effects against diarrhea in mice [41], inhibition of bronchospasms provoked by chemical irritants in rats [145], and stabilization of respiration in sleep-related breathing disorders (e.g. apnea) [146]. Animal research has demonstrated that CB₁-deficient mice showed strongly impaired short-term and long-term extinction of aversive memories [147], which may explain some of the anxiety reducing effects in posttraumatic stress disorder and similar conditions [148].

Conclusions

Mechanisms of action of cannabinoids are complex, not only involving activation of and interaction at the cannabinoid receptor, but also activation of vanilloid receptors, influence of endocannabinoid concentration, antioxidant activity, 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, together with the large body of multidisciplinary research efforts from recent decades, we do not expect to encounter the same unpleasant surprises with the medicinal use of cannabinoids, which occur occasionally with newly designed synthetic drugs.

Aside from phytocannabinoids and cannabis preparations, cannabinoid analogues that do not bind to the CB₁ receptor are attractive compounds for clinical research, among them dexanabinol, HU-308 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 CB₁ 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).

It can be expected that within a decade several cannabinoids and modulators of the cannabinoid system will find their way from preclinical research into the pharmacies.

REFERENCES

- 1 Loewe S. Cannabiswirkstoffe und Pharmakologie der Cannabinoide [(Active constituents of cannabis and pharmacology of the cannabinoids.) (In German.)]. *Archiv für Experimentelle Pathologie und Pharmakologie* 1950; **211**:175–93.
- 2 Dewey WL. Cannabinoid pharmacology. *Pharmacol Rev* 1986; **38**:151–78.

- 3 Hollister LE. Health aspects of cannabis. *Pharmacological Reviews* 1986; **38**:1–20.
- 4 ElSohly MA. Chemical constituents of cannabis. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press; 2002. p 27–36.
- 5 McPartland JM, Russo EB. Cannabis and Cannabis Extracts: Greater Than the Sum of Their Parts? *J Cannabis Ther* 2001; **1**: 103–32.
- 6 Bueb JL, Lambert DM, Tschirhart EJ. Receptor-independent effects of natural cannabinoids in rat peritoneal mast cells in vitro. *Biochim Biophys Acta* 2001; **1538**:252–9.
- 7 Hampson A. Cannabinoids as neuroprotectants against ischemia. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press; 2002. p. 101–10.
- 8 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; **6**:245–50.
- 9 Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* 2001; **134**:845–52.
- 10 Costa B, Parolaro D, Colleoni M. Chronic cannabinoid, CP-55,940, administration alters biotransformation in the rat. *Eur J Pharmacol* 1996; **313**:17–24.
- 11 Mechoulam R, Hanus L. Cannabidiol: an overview of some chemical and pharmacological aspects. Part I: chemical aspects. *Chem Phys Lipids* 2002; **121**:35–43.
- 12 Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metab Dispos* 1995; **23**:825–31.
- 13 Bornheim LM, Grillo MP. Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of cannabidiol-hydroxyquinone as a P450 inactivator. *Chem Res Toxicol* 1998; **11**:1209–16.
- 14 Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB₂ receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998; **76**:189–99.
- 15 Agurell S, Carlsson S, Lindgren JE, Ohlsson A, Gillespie H, Hollister L. Interactions of delta 1-tetrahydrocannabinol with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography. *Experientia* 1981; **37**:1090–2.
- 16 Hunt CA, Jones RT, Herning RI, Bachman J. Evidence that cannabidiol does not significantly alter the pharmacokinetics of tetrahydrocannabinol in man. *J Pharmacokinet Biopharm* 1981; **9**:245–60.
- 17 Pertwee RG. Pharmacology of cannabinoid CB₁ and CB₂ receptors. *Pharmacol Ther* 1997; **74**:129–80.
- 18 Howlett AC. The cannabinoid receptors. *Prostaglandins Other Lipid Mediat* 2002; **68–69**:619–31.
- 19 Pertwee RG. Sites and Mechanisms of Action. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press; 2002. p. 73–88.
- 20 Hanus L, Breuer A, Tchilibon S, Shiloah S, Goldenberg D, Horowitz M, Pertwee RG, Ross RA, Mechoulam R, Fride E. HU-308: a specific agonist for CB₂, a peripheral cannabinoid receptor. *Proc Natl Acad Sci U S A* 1999; **96**:14228–33.
- 21 Sanchez C, de Ceballos ML, del Pulgar TG, Rueda D, Corbacho C, Velasco G, et al. Inhibition of glioma growth in vivo by selective activation of the CB₂ cannabinoid receptor. *Cancer Res* 2001; **61**:5784–9.
- 22 Breivogel CS, Griffin G, Di Marzo V, Martin BR. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. *Mol Pharmacol* 2001; **60**:155–63.
- 23 Di Marzo V, Hill MP, Bisogno T, Crossman AR, Brotchie JM. Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. *FASEB J* 2000; **14**:1432–8.

- 24 Fride E, Fox A, Rosenberg E, Faigenboim M, Cohen V, Barda L, et al. Milk intake and survival in newborn cannabinoid CB1 receptor knockout mice: evidence for a "CB3" receptor. *Eur J Pharmacol* 2003; **461**:27–34.
- 25 Wiley JL, Martin BR. Cannabinoid pharmacology: implications for additional cannabinoid receptor subtypes. *Chem Phys Lipids* 2002; **121**:57–63.
- 26 Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992; **258**:1946–9.
- 27 Giuffrida A, Beltramo M, Piomelli D. Mechanisms of endocannabinoid inactivation: biochemistry and pharmacology. *J Pharmacol Exp Ther* 2001; **298**:7–14.
- 28 Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K Yamashita A, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun* 1995; **215**:89–97.
- 29 Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* 1995; **50**:83–90.
- 30 Hanus L, Abu-Lafi S, Fride E, Breuer A, Vogel Z, Shalev DE, et al. 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. *Proc Natl Acad Sci U S A* 2001; **98**:3662–5.
- 31 Porter AC, Sauer JM, Knierman MD, Becker GW, Berna MJ, Bao J, et al. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor. *J Pharmacol Exp Ther* 2002; **301**:1020–4.
- 32 Huang SM, Bisogno T, Trevisani M, Al-Hayani A, De Petrocellis L, Fezza F, et al. An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors. *Proc Natl Acad Sci U S A* 2002; **99**:8400–5.
- 33 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**:377–87.
- 34 Al-Hayani A, Wease KN, Ross RA, Pertwee RG, Davies SN. The endogenous cannabinoid anandamide activates vanilloid receptors in the rat hippocampal slice. *Neuropharmacology* 2001; **41**:1000–1005.
- 35 Di Marzo V. 'Endocannabinoids' and other fatty acid derivatives with cannabimimetic properties: biochemistry and possible physiopathological relevance. *Biochim Biophys Acta* 1998; **1392**:153–75.
- 36 Dinh TP, Freund TF, Piomelli D. A role for monoglyceride lipase in 2-arachidonoylglycerol inactivation. *Chem Phys Lipids* 2002; **121**:149–58.
- 37 Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998; **76**:189–99.
- 38 Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci U S A* 1999; **96**:12198–203.
- 39 Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Makriyannis A, et al. Endocannabinoids control spasticity in a multiple sclerosis model. *FASEB J* 2001; **15**:300–2.
- 40 Siegling A, Hofmann HA, Denzer D, Mauler F, De Vry J. Cannabinoid CB(1) receptor upregulation in a rat model of chronic neuropathic pain. *Eur J Pharmacol* 2001; **415**:R5–R7.
- 41 Izzo AA, Pinto L, Borrelli F, Capasso R, Mascolo N, Capasso F. Central and peripheral cannabinoid modulation of gastrointestinal transit in physiological states or during the diarrhoea induced by croton oil. *Br J Pharmacol* 2000; **129**:1627–32.
- 42 Di Marzo V, Goparaju SK, Wang L, Liu J, Batkai S, Jarai Z, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 2001; **410**:822–5.
- 43 Darmani NA. Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB(1) receptors in the least shrew. *Pharmacol Biochem Behav* 2001; **69**:239–49.
- 44 Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 1996; **91**:1585–614.
- 45 Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002.
- 46 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.
- 47 House of Lords Select Committee on Science and Technology. Cannabis. The scientific and medical evidence. London: The Stationery Office; 1998.
- 48 Joy JE, Watson SJ, Benson JA, editors. Marijuana and medicine: Assessing the science base. Washington DC: Institute of Medicine, National Academy Press; 1999.
- 49 Kalant H, Corrigal W, Hall W, Smart R, editors. The health effects of cannabis. Toronto (Canada): Centre for Addiction and Mental Health; 1999.
- 50 Sulcova E, Mechoulam R, Fride E. Biphasic effects of anandamide. *Pharmacol Biochem Behav* 1998; **59**:347–52.
- 51 Thompson GR, Rosenkrantz H, Schaeppi UH, Braude MC. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. *Toxicol Appl Pharmacol* 1973; **25**:363–72.
- 52 Bachs L, Morland H. Acute cardiovascular fatalities following cannabis use. *Forensic Sci Int* 2001; **124**:200–3.
- 53 Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation* 2001; **103**:2805–9.
- 54 Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry* 2001; **58**:909–15.
- 55 Pope HG Jr. Cannabis, cognition, and residual confounding. *JAMA* 2002; **287**:1123–31.
- 56 Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, et al. Cognitive functioning of Long-term Heavy Cannabis Users Seeking Treatment. *JAMA* 2002; **287**:1123–31.
- 57 Lyketsos CG, Garrett E, Liang KY, Anthony JC. Cannabis use and cognitive decline in persons under 65 years of age. *Am J Epidemiol* 1999; **149**:794–800.
- 58 Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend* 2003; **69**:303–10.
- 59 Russo E, Mathre ML, Byrne A, Velin R, Bach PJ, Sanchez-Ramos J, et al. Chronic cannabis use in the compassionate investigational new drug program: An examination of benefits and adverse effects of legal medical cannabis. *J Cannabis Ther* 2002; **2**:3–57.
- 60 Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol* 1998; **20**:293–306.
- 61 Solowij N, Grenyer BFS. Long term effects of cannabis on psyche and cognition. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 299–312.
- 62 Nunez LA, Gurpegui M. Cannabis-induced psychosis: a cross-sectional comparison with acute schizophrenia. *Acta Psychiatr Scand* 2002; **105**:173–8.
- 63 Mattes RD, Shaw LM, Engelman K. Effects of cannabinoids (marijuana) on taste intensity and hedonic ratings and salivary flow of adults. *Chem Senses* 1994; **19**:125–40.
- 64 Freeman FR. Effects of marijuana on sleeping states. *JAMA* 1972; **220**:1364–5.
- 65 Lissoni P, Resentini M, Mauri R, Esposti D, Esposti G, Rossi D, et al. Effects of tetrahydrocannabinol on melatonin secretion in man. *Horm Metab Res* 1986; **18**:77–8.
- 66 Hampson RE, Deadwyler SA. Cannabinoids, hippocampal function and memory. *Life Sci* 1999; **65**:715–23.
- 67 Heyser CJ, Hampson RE, Deadwyler SA. Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: alterations in short-term memory associated with changes in task specific firing of hippocampal cells. *J Pharmacol Exp Ther* 1993; **264**:294–307.
- 68 Slikker W Jr, Paule MG, Ali SF, Scallet AC, Bailey JR. Behavioral, neurochemical and neurohistochemical effects of chronic marijuana smoke exposure in the nonhuman primate. In: Myrphy L,

- Bartke A, editors. Marijuana/Cannabinoids: neurobiology and neurophysiology. Boca Raton, FL: CRC Press; 1992. p. 219–73.
- 69 Müller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. *Neuropsychopharmacology* 2003; **28**:384–8.
- 70 Pertwee R. In vivo interactions between psychotropic cannabinoids and other drugs involving central and peripheral neurochemical mediators. In: Murphy L, Bartke A, editors. Marijuana/Cannabinoids: neurobiology and neurophysiology. Boca Raton, FL: CRC Press; 1992. p. 165–218.
- 71 Baker D, Pryce G, Giovannoni G, Thompson AJ. The therapeutic potential of cannabis. *Lancet Neurol* 2003; **2**:291–8.
- 72 Domino EF. Cannabinoids and the cholinergic system. In: Nahas G, Sutin KM, Harvey DJ, Agurell S, editors. Marijuana and medicine. Totowa, NJ: Humana Press; 1999. p. 223–6.
- 73 Fan P. Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion neurons. *J Neurophysiol* 1995; **73**:907–10.
- 74 Müller-Vahl KR, Kolbe H, Schneider U, Emrich HM. Movement Disorders. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 205–214.
- 75 Musty RE, Paul Consroe P. Spastic disorders. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 195–204.
- 76 Lichtman AH, Peart J, Poklis JL, Bridgen DT, Razdan RK, Wilson DM, Poklis A, Meng Y, Byron PR, Martin BR. Pharmacological evaluation of aerosolized cannabinoids in mice. *Eur J Pharmacol* 2000; **399**:141–9.
- 77 Braidà D, Pozzi M, Cavallini R, Sala M. Conditioned place preference induced by the cannabinoid agonist CP 55,940: interaction with the opioid system. *Neuroscience* 2001; **104**:923–6.
- 78 Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science* 1997; **276**:2048–50.
- 79 Wachtel SR, de Wit H. Naltrexone does not block the subjective effects of oral delta(9)-tetrahydrocannabinol in humans. *Drug Alcohol Depend* 2000; **59**:251–60.
- 80 Haney M, Bisaga A, Foltin RW. Interaction between naltrexone and oral THC in heavy marijuana smokers. *Psychopharmacology (Berl)* 2003; **166**:77–85.
- 81 Mechoulam R, Shohami E. HU-211: Cannabinoid Neuroprotective Agent. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 389–400.
- 82 Grundy RI. The therapeutic potential of the cannabinoids in neuroprotection. *Expert Opin Investig Drugs* 2002; **11**:1365–74.
- 83 Van der Stelt M, Veldhuis WB, Bar PR, Veldink GA, Vliegenthart JF, Nicolay K. Neuroprotection by Delta9-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. *J Neurosci* 2001; **21**:6475–9.
- 84 Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, Biegan A. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. *Crit Care Med* 2002; **30**:548–54.
- 85 Perez-Reyes M. The psychologic and physiologic effects of active cannabinoids. In: Nahas G, Sutin KM, Harvey DJ, Agurell S. Marijuana and medicine. Totowa, NJ: Humana Press; 1999. p. 245–52.
- 86 Tashkin DP, Levisman JA, Abbasi AS, Shapiro BJ, Ellis NM. Short-term effects of smoked marijuana on left ventricular function in man. *Chest* 1977; **72**:20–6.
- 87 Benowitz NL, Jones RT. Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clin Pharmacol Ther* 1975; **18**:287–97.
- 88 Szabo B, Nordheim U, Niederhoffer N. Effects of cannabinoids on sympathetic and parasympathetic neuroeffector transmission in the rabbit heart. *J Pharmacol Exp Ther* 2001; **297**:819–26.
- 89 Lake KD, Compton DR, Varga K, Martin BR, Kunos G. cannabinoid-induced hypotension and bradycardia in rats is mediated by CB1-like cannabinoid receptors. *J Pharmacol Exp Ther* 1997; **281**:1030–7.
- 90 Wagner JA, Varga K, Kunos G. Cardiovascular actions of cannabinoids and their generation during shock. *J Mol Med* 1998; **76**:824–36.
- 91 Wagner JA, Jarai Z, Batkai S, Kunos G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB1 receptors. *Eur J Pharmacol* 2001; **423**:203–10.
- 92 Williams CM, Kirkham TC. Observational analysis of feeding induced by Delta(9)-THC and anandamide. *Physiol Behav* 2002; **76**:241–50.
- 93 Mechoulam R, Shohami E, Fride E, Bab I. The ubiquitous role of endocannabinoids in physiological processes: examples in neuroprotection, feeding and bone formation. First European Workshop on Cannabinoid Research. Madrid (Spain); 2003.
- 94 De Petrocellis L, Melck D, Palmisano A, Bisogno T, Laezza C, Bifulco M, Di Marzo V. The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. *Proc Natl Acad Sci U S A* 1998; **95**:8375–80.
- 95 Melck D, De Petrocellis L, Orlando P, Bisogno T, Laezza C, Bifulco M, Di Marzo V. Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation. *Endocrinology* 2000; **141**:118–26.
- 96 Galve-Roperh I, Sanchez C, Cortes ML, del Pulgar TG, Izquierdo M, Guzman M. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nat Med* 2000; **6**:313–9.
- 97 Shook JE, Burks TF. Psychoactive cannabinoids reduce gastrointestinal propulsion and motility in rodents. *J Pharmacol Exp Ther* 1989; **249**:444–9.
- 98 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. *Aliment Pharmacol Ther* 1999; **13**:77–80.
- 99 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 anesthetized rat. *Naunyn Schmiedebergs Arch Pharmacol* 1999; **360**:715–8.
- 100 Pate D. Glaucoma and cannabinoids. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 215–24.
- 101 Laine K, Jarvinen K, Jarvinen T. Topically administered CB(2)-receptor agonist, JWH-133, does not decrease intraocular pressure (IOP) in normotensive rabbits. *Life Sci* 2003; **72**:837–42.
- 102 Murphy L. Hormonal system and reproduction. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 289–98.
- 103 Cabral G. Immune system. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 279–88.
- 104 Melamed R. Possible mechanisms in autoimmune diseases. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 111–22.
- 105 Yuan M, Kiertscher SM, Cheng Q, Zoumalan R, Tashkin DP, Roth MD. Delta 9-Tetrahydrocannabinol regulates Th1/Th2 cytokine balance in activated human T cells. *J Neuroimmunol* 2002; **133**:124–31.
- 106 Hembree WC 3d, Nahas GG, Zeidenberg P, Huang HF. Changes in human spermatozoa associated with high dose marijuana smoking. *Adv Biosci* 1978; **22–23**:429–39.
- 107 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. *Mol Reprod Dev* 1993; **36**:507–16.
- 108 Zuardi AW, Guimarães FS, Guimarães VMC, Del Bel EA. Cannabinoid: Possible therapeutic application. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Binghamton (NY): Haworth Press; 2002. p. 359–70.

- 109 Karler R, Turkanis SA. The cannabinoids as potential antiepileptics. *J Clin Pharmacol* 1981; **21**(8-9 Suppl):437S-48S.
- 110 Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. *Int J Neurosci* 1986; **30**: 277-82.
- 111 Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *Neuroreport* 2002; **13**:567-70.
- 112 Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreanos E, Mechoulam R, Feldmann M. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritis therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci U S A* 2000; **97**:9561-6.
- 113 Colasanti BK, Brown RE, Craig CR. Ocular hypotension, ocular toxicity, and neurotoxicity in response to marihuana extract and cannabidiol. *Gen Pharmacol* 1984; **15**:479-84.
- 114 Archer RA, Stark P, Lemberger L, Nabilone. In: Mechoulam R, editors. *Cannabinoids as therapeutic agents*. Boca Raton: CRC Press; 1986. p. 85-103.
- 115 Burstein S. Therapeutic potential of ajulemic acid (CT3). In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential*. Binghamton (NY): Haworth Press; 2002. p. 381-8.
- 116 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. *J Pharmacol Exp Ther* 1995; **272**: 699-707.
- 117 Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ. Effects of chronic exposure to Δ^9 -tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Brain Res Mol Brain Res* 1997; **46**:100-8.
- 118 Di Marzo V, Berrendero F, Bisogno T, Gonzalez S, Cavaliere P, Romero J, Cebeira M, Ramos JA, Fernandez-Ruiz JJ. Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of Δ^9 -tetrahydrocannabinol-tolerant rats. *J Neurochem* 2000; **74**: 1627-35.
- 119 Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci* 1976; **282**: 221-39.
- 120 Rubino T, Vigano D, Massi P, Parolaro D. Changes in the cannabinoid receptor binding, G protein coupling, and cyclic AMP cascade in the CNS of rats tolerant to and dependent on the synthetic cannabinoid compound CP55,940. *J Neurochem* 2000; **75**:2080-6.
- 121 Georgotas A, Zeidenberg P. Observations on the effects of four weeks of heavy marihuana smoking on group interaction and individual behavior. *Compr Psychiatry* 1979; **20**:427-32.
- 122 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 Clin Psychopharmacol* 1994; **2**:244-68.
- 123 Kleiber D, Soellner R, Tossmann P. Cannabiskonsum in der Bundesrepublik Deutschland: Entwicklungstendenzen, Konsummuster und Einflussfaktoren [(Cannabis consumption in the Federal Republic of Germany: Development tendencies, consumption pattern and influential factors. (In German with English abstract.)). Bonn: Federal Ministry of Health; 1997.
- 124 Roques B. Problemes posées par la dangerosité des drogues. Rapport du professeur Bernhard Roques au Secrétaire d'Etat à la Santé [Problems caused by the danger of drugs. Report of professor Bernhard Roques to the Health Minister.] (In French.)). Paris; 1998.
- 125 Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol®). *J Psychoactive Drugs* 1998; **30**:187-96.
- 126 Lane M, Vogel CL, Ferguson J, Krasnow S, Sainers JL, Hamm J, Salva K, Wiernik PH, Holroyde CP, Hammill S, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J Pain Symptom Manage* 1991; **6**(6):352-9
- 127 Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokin* 2003; **42**(4):327-360.
- 128 Cichewicz DL, McCarthy EA. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther* 2003; **304**:1010-5.
- 129 Koe BK, Milne GM, Weissman A, Johnson MR, Melvin LS. Enhancement of brain [3H]flunitrazepam binding and analgesic activity of synthetic cannabimimetics. *Eur J Pharmacol* 1985; **109**:201-12.
- 130 Perez-Reyes M, Burstein SH, White WR, McDonald SA, Hicks RE. Antagonism of marihuana effects by indomethacin in humans. *Life Sci* 1991; **48**:507-15.
- 131 Bonz A, Laser M, Kullmer S, Kniesch S, Babin-Ebell J, Popp V, Ertl G, Wagner JA. Cannabinoids acting on CB1 receptors decrease contractile performance in human atrial muscle. *J Cardiovasc Pharmacol* 2003; **41**:657-64.
- 132 Green K, Kearse EC, McIntyre OL. Interaction between delta-9-tetrahydrocannabinol and indomethacin. *Ophthalmic Res* 2001; **33**:217-20.
- 133 British Medical Association. *Therapeutic uses of cannabis*. Amsterdam: Harwood Academic Publishers; 1997.
- 134 Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine*. New Haven: Yale University Press; 1993.
- 135 Mechoulam R, editor. *Cannabinoids as therapeutic agents*. Boca Raton: CRC Press; 1986.
- 136 Bagshaw SM, Hagen NA. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. *J Palliat Care* 2002; **18**:111-22.
- 137 Grotenhermen F. *Clinical Pharmacodynamics of Cannabinoids*. *J Cannabis Ther* 2004, in press.
- 138 Jan TR, Farraj AK, Harkema JR, Kaminski NE. Attenuation of the ovalbumin-induced allergic airway response by cannabinoid treatment in A/J mice. *Toxicol Appl Pharmacol*. 2003; **188**: 24-35.
- 139 Chan PC, Sills RC, Braun AG, Haseman JK, Bucher JR. Toxicity and carcinogenicity of delta 9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice. *Fundam Appl Toxicol* 1996; **30**:109-17.
- 140 Casanova ML, Blazquez C, Martinez-Palacio J, Villanueva C, Fernandez-Acenero MJ, Huffman JW, Jorcano JL, Guzman M. Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. *J Clin Invest* 2003; **111**: 43-50.
- 141 Blazquez C, Casanova ML, Planas A, Del Pulgar TG, Villanueva C, Fernandez-Acenero MJ, Aragonés J, Huffman JW, Jorcano JL, Guzman M. Inhibition of tumor angiogenesis by cannabinoids. *FASEB J* 2003; **17**:529-31.
- 142 Ralevic V, Kendall DA. Cannabinoid inhibition of capsaicin-sensitive sensory neurotransmission in the rat mesenteric arterial bed. *Eur J Pharmacol* 2001; **418**:117-25.
- 143 Wagner JA, Jarai Z, Batkai S, Kunos G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB(1) receptors. *Eur J Pharmacol* 2001; **423**: 203-10.
- 144 Wagner JA, Hu K, Karcher J, Bauersachs J, Schafer A, Laser M, Han H, Ertl G. CB1 cannabinoid receptor antagonism promotes remodeling and cannabinoid treatment prevents endothelial dysfunction and hypotension in rats with myocardial infarction. *Br J Pharmacol* 2003, in press.
- 145 Calignano A, Katona I, Desarnaud F, Giuffrida A, La Rana G, Mackie K, Freund TF, Piomelli D. Bidirectional control of airway responsiveness by endogenous cannabinoids. *Nature* 2000; **408**:96-101.
- 146 Carley DW, Paviovic S, Janelidze M, Radulovacki M. Functional role for cannabinoids in respiratory stability during sleep. *Sleep* 2002; **25**:391-8.
- 147 Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, Hermann H, Tang J, Hofmann C, Zieglgansberger W, Di Marzo V, Lutz B. The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 2002; **418**:488-9.
- 148 Sah P. Never fear, cannabinoids are here. *Nature* 2002; **418**: 488-9.