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REVIEW ARTICLE

Pharmacology of Cannabinoids

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Abstract

Dronabinol (Δ^9-tetrahydocannabinol, THC), the main source of the pharmacological effects caused by the use of cannabis, is an agonist to both the CB_1 and the CB_2 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 Marinol™. 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 CB_1 receptor and was able to inhibit several CB_1 mediated THC effects [8]. In a study by Petitet et al. (1998), CBD considerably reduced the receptor activation of a potent classical CB_1 receptor agonist.

(2) CBD stimulates the vanilloid receptor type 1 (VR_1) 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 CB_1 (cloned in 1990), and the CB_2 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.

CB_1 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]. 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 [18], which may account for the lack of cannabis-related acute fatalities, e.g. due to depression of respiration.

CB_2 receptors are located principally in immune cells, among them leukocytes, spleen and tonsils [19]. Immune cells also express CB_1 receptors but there is markedly more mRNA for CB_2 than CB_1 receptors in the immune system. 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 [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*-arachidonylethanolamide (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 (VR_1) [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 effects 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 (LD_{50}) 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]. Marihuana 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-HT_3 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 CB_1 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 sympathicus, obviously by activation of CB_1 receptors since this effect can also be prevented by a CB_1 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 CB_1 receptors [91].

TABLE 1. 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 homoeostasis, hormones, depression
Serotonin	Depression, anxiety, migraine, vomiting
Dopamine	Parkinson's disease, schizophrenia, vomiting, pituitary hormones, drug addiction
Acetylcholine	Neuromuscular disorders, autonomic homoeostasis (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 CB_1 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 CB_2 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]. CB_1 receptors in the eye are involved in this effect while CB_2 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 inflammation 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 Δ^8-THC metabolite THC-COOH, is under clinical investigation for inflammation and pain [115].

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 [116], and very low doses of anandamide antagonized the actions of THC. Anandamide also stimulates the vanilloid receptor (VR_1) [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 down-regulation 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 hierarchy 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 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 [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 CB_1-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 CB_1 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 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).

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

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