Cannabinoids

Franjo Grotenhermen*

Nova-Institut, Goldenbergstraße 2, D-50354 Hürth, Germany

Abstract: Since the discovery of an endogenous cannabinoid system, research into the pharmacology and therapeutic potential of cannabinoids has steadily increased. Two subtypes of G-protein coupled cannabinoid receptors, CB_1 and CB_2, have been cloned and several putative endogenous ligands (endocannabinoids) have been detected during the past 15 years. The main endocannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), derivatives of arachidonic acid, that are produced "on demand" by cleavage of membrane lipid precursors. Besides phytocannabinoids of the cannabis plant, modulators of the cannabinoid system comprise synthetic agonists and antagonists at the CB receptors and inhibitors of endocannabinoid degradation. Cannabinoid receptors are distributed in the central nervous system and many peripheral tissues, including immune system, reproductive and gastrointestinal tracts, sympathetic ganglia, endocrine glands, arteries, lung and heart. There is evidence for some non-receptor dependent mechanisms of cannabinoids and for endocannabinoid effects mediated by vanilloid receptors.

Properties of CB receptor agonists that are of therapeutic interest include analgesia, muscle relaxation, immunosuppression, anti-inflammation, antiallergic effects, improvement of mood, stimulation of appetite, antiemesis, lowering of intraocular pressure, bronchodilation, neuroprotection and antineoplastic effects. The current main focus of clinical research is their efficacy in chronic pain and neurological disorders. CB receptor antagonists are under investigation for medical use in obesity and nicotine addiction. Additional potential was proposed for the treatment of alcohol and heroine dependency, schizophrenia, conditions with lowered blood pressure, Parkinson's disease and memory impairment in Alzheimer's disease.

Keywords: Cannabis, THC, cannabinoids, cannabinoid receptors, endocannabinoids, cannabinoid receptor antagonists, therapeutic potential, side effects.

1. INTRODUCTION

Despite a long history of medicinal use lasting back more than 4,000 years [1, 2], the introduction of cannabinoids into modern medicine is only beginning. Unlike opiates and many other plant constituents used for therapeutic purposes, the most active ingredient Δ^9-tetrahydrocannabinol (Δ^9-THC, dronabinol) was been identified only 40 years ago (see Fig. **1**). In addition, less than 20 years have passed since the detection of an endogenous system of specific receptors and their endogenous ligands, the "endocannabinoid system" or "cannabinoid system".

In the 1930s and 1940s, the chemical structure of the first phytocannabinoids had been successfully characterized [3], and the first synthetic derivatives of THC (parahexyl, DMHP) were successfully tested in clinical studies for epilepsy [4], depression [5] and dependency to alcohol and opiates [6]. However, it was not until 1964 that Δ^9-THC was stereochemically defined and synthesized [7].

Both discoveries, the identification of THC, which allowed basic and clinical studies with defined and reproducible doses, and the detection of the endocannabinoid system in mammals, which allowed the investigation of mechanisms of cannabinoid actions and the exploration of the therapeutic potential of inhibitors of endocannabinoid degradation and cannabinoid receptor antagonists, resulted in a considerable boost in research activities. The number of publications listed in the database PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) rose from very few to about 400 per year in 1972, then declined to 250 in 1982, remained at this level until 1989, and then steadily rose to about 1100 per year in 2004.

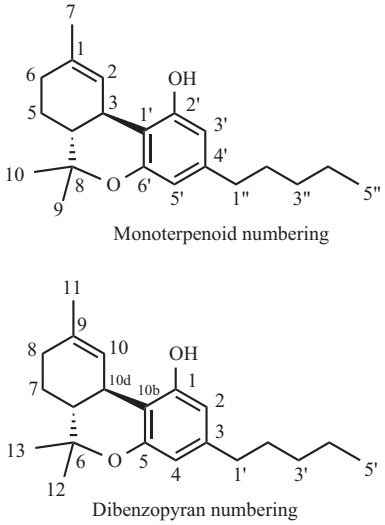

Fig. (1). Chemical structure of THC, the main cannabinoid in the cannabis plant, according to the monoterpenoid system (Δ^1-THC) and dibenzopyran system (Δ^9-THC).

*Address correspondence to the author at the Nova-Institut, Goldenbergstraße 2, D-50354 Hürth, Germany Tel: +49-2247-968085; Fax: +49-2247-9159223; E-mail: franjo.grotenhermen@nova-institut.de

1568-007X/05 $50.00+.00

2. CANNABINOID RECEPTORS

To date, two cannabinoid receptors have been identified, the CB_1 (cloned in 1990) [8], and the CB_2 receptor (cloned in 1993) [9], 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 may show marked selectivity for one or the other receptor type [10].

Activation of the CB_1 receptor produces effects on circulation and psychotropic effects common to cannabis ingestion, 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 being analgesic, anti-inflammatory and anti-neoplastic actions [11, 12].

2.1. Genetics

The endocannabinoid system is teleologically, millions of years old and has been found in mammals, birds, amphibians, fish, sea urchins, molluscs, leeches and even primitive Hydra vulgaris [13, 14]. The nucleotide sequences of genes encoding the cannabinoid receptors vary from species to species, their identity with the human CB sequence being proportional to the evolutionary distances between the organisms. The CB_1 gene (CNR_1) of the rhesus monkey (Macaca mulata) is 100% identical to the sequence of the human CNR_1, whereas the CB_1 gene of the leech (Hirudo medicinalis) shares only 58% of the human gene [14]. Comparisons between human, rat and mouse CB_1 receptor sequences showed extensive homology both at the nucleotide and protein levels [15]. The CB_1-receptor nucleotide sequences of humans and rats are 90% and those of humans and mice are 91% identical. CB_2 receptors show greater interspecies differences with a similarity of 82% between the mouse and human receptor protein, the human CB_2 being 13 amino acids longer at the carboxyl terminus [16] and 81% amino acid homology between the rat and human CB_2 receptor [17]. Pronounced species selectivity at the rat cannabinoid CB_2 receptor compared to the human CB_2 receptor was observed for two synthetic cannabinoids (AM-1710 and AM-1714), whereas JWH-015 and endocannabinoids were more human receptor selective [17]. These findings of pharmacological species differences are critical for characterizing cannabinoid receptor ligands in *in vivo* rodent models for drug discovery purpose.

A first spliced amino-truncated variant (isoform) of the CB_1 receptor cDNA, CB_{1a}, has been isolated by Rinaldi-Carmona *et al.* (1996) [19]. Recently, another group reported the detection of another spliced variant (CB_{1b}) and noted that both variants have a unique pharmacological profile and that their RNA's are expressed at low levels in several tissues [19].

Attempts have been made to investigate a possible association between the predisposition to certain diseases and mutations or variants in the CB_1 receptor gene. Schizophrenia [20] and depression in Parkinson's disease [21] may be related to a genetic polymorphism of the CNR_1, while Tourette's syndrome and delirium tremens in alcoholism [22] do not seem to be associated with a mutation of the CB_1 receptor gene [23]. Individuals with a 9-repeat allele of an AAT-repeat polymorphism of the gene may have a 2.3-fold higher susceptibility to schizophrenia [20].

Both CB_1 and CB_2 receptors belong to the class A (rhodopsin like) G-protein-coupled receptors (GPCR). G-proteins coupled to cannabinoid receptors are sensitive to pertussis toxin, an inactivator of inhibiting G_i and G_o proteins. Among the class A GPCRs are receptors for melatonin, thyrotropin-releasing hormone, prostanoid and the leukotriene B4 receptor. GPCRs are the most common receptors, containing 1000-2000 members in vertebrates (>1% of the genome) [24]. GPCRs are involved in the recognition and transduction of messages as diverse as light, Calcium ions, odorants, nucleotides and peptides, as well as proteins, controlling the activity of enzymes, ion channels and transport of vesicles [24].

2.2. Distribution

CB_1 receptors are mainly found on neurons in the brain, spinal cord and peripheral nervous system, but are also present in certain peripheral organs and tissues, among them being immune cells, spleen, adrenal and pituitary glands, sympathetic ganglia, heart, lung and parts of the reproductive, urinary and gastrointestinal tracts [25]. In the central nervous system, the CB_1 receptor is the most abundant G-protein coupled receptor.

CB_1 receptors are highly expressed in the cerebral cortex, basal ganglia (substantia nigra pars reticulata, globus pallidus, nucleus caudatus and putamen) cerebellum, hippocampus, periaqueductal grey, rostral ventromedial medulla, certain nuclei of the thalamus and amygdala, 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 [10], which may account for the lack of cannabis-related acute fatalities, e.g. due to depression of respiration. Many CB_1 receptors are expressed at the terminals of central and peripheral nerves and inhibit the release of neurotransmitters.

CB_1 receptors have also been found at the central and peripheral terminals of small diameter C-fibers and larger diameter Aβ/Aδ-fibers of primary afferent neurons. This helps to explain the efficacy of CB_1 receptor agonists in neuropathic pain, since this kind of pain is thought to be elicited in part by abnormal spontaneous discharges of Aβ and Aδ fibers [26].

CB_2 receptors occur principally in immune cells, among them being leukocytes, spleen and tonsils [27]. Immune cells also express CB_1 receptors, but there is markedly more mRNA for CB_2 than CB_1 receptors in the immune system. Levels of CB_1 and CB_2 mRNA in human leukocytes have been shown to vary with cell type (B cells > natural killer cells > monocytes > polymorphonuclear neutrophils, T4 and T8 cells) [28]. One of the functions of CB receptors in the immune system is modulation of cytokine release. Activation of CB_2 receptors has also been reported to produce antinociception, by stimulating peripheral release of endogenous opioids [29].

2.3. Mechanisms of Action

Agonistic stimulation of both types of cannabinoid receptors activates a number of signal transduction pathways [25, 27]. Both are coupled through inhibiting G-proteins ($G_{i/o}$ proteins), negatively to adenylate cyclase and positively to mitogen-activated protein kinase. Inhibition of adenylate cyclase results in the inhibition of the conversion of ATP to cyclic AMP (cAMP). CB_1, but not CB_2 receptors are also coupled to several ion channels through $G_{i/o}$ proteins, negatively to N-type and P/Q-type calcium channels and D-type potassium channels, positively to A-type and inwardly rectifying potassium channels. CB_1 receptors may also mobilize arachidonic acid, close 5-HT_3 receptors ion channels, modulate nitric oxide production and mobilize arachidonic acid and intracellular calcium stores [26]. CB_1 receptor activation can also initiate ceramide production through a non-G protein mediated mechanism, and under certain conditions, CB_1 receptors may also activate adenylate cyclase and/or reduce outward potassium K current through stimulating G proteins (G_s proteins) [26].

In vitro experiments have demonstrated that CB_1 receptors can mediate inhibition of the neuronal release of a multitude of neurotransmitters and neuromodulators, including acetylcholine, dopamine, γ-aminobutyric acid (GABA), histamine, serotonin (5-hydroxytryptamine), glutamate, cholecystokinin, D-aspartate, glycine and noradrenaline (norepinephrine) in several brain regions and outside the brain (see Table **1**). Inhibition of neurotransmitters by CB_1 receptor activation in the central nervous system is caused by presynaptic inhibition of neurotransmitter release from axon terminals [30]. In the CNS, this inhibition is caused by both endocannabinoids and exogenous cannabinoids. Presynaptic inhibition of neurotransmitters by exogenous cannabinoids that bind to the peripheral CB_1 receptor has also been described in the sympathetic nervous system, but endocannabinoid-mediated presynaptic inhibition was not observed in all assays investigating their action in the sympathetic nervous system [30].

In some experiments, CB_1 receptor agonists have been reported not to inhibit but to enhance the release of certain neurotransmitters. However, it is possible that these effects also result from a CB receptor-mediated inhibitory effect on neurotransmitter release, resulting in a stimulatory effect on neurotransmitter release at some point downstream of the side of the initial inhibitory effect [26].

Interaction of THC effects with other neurotransmitters is supported by the fact that antagonists of these neurotransmitters blocked specific THC effects. The memory disruptive effects of THC were completely reversed by the GABA antagonist bicuculline, while other THC effects were unaffected [31]. Opioid receptor antagonists blocked several behavioral effects of CB_1 agonists [32, 33]. A number of pharmacological effects can be explained (at least in part) on the basis of interactions with other neurotransmitters. For example, tachycardia and hyposalivation with dry mouth [34, 35] are mediated by effects of THC on release and turn-over of acetylcholine [34]. In a rat model, cannabinoid agonists inhibited activation of 5-HT_3 receptors, explaining antiemetic properties of cannabinoids to be based on interactions with serotonin [36]. Therapeutic effects in movement and spastic disorders could be ascribed in part to interactions with GABAergic, glutamergic and dopaminergic transmitters systems [37]. The effects on GABA, glutamate and glycine release in the periaqueductal grey, rostral ventromedial medulla and substantia nigra may contribute to the modulation of pain perception.

Cannabinoids may cause contradictory effects with suppression or induction/intensification of somatic and psychic effects, including convulsion, emesis, pain, tremor and anxiety, depending on subject and condition. Cannabis and THC are used against nausea and vomiting caused by anti-neoplastic drugs but may rarely cause vomiting. They are used as analgesics but sometimes may increase pain [38]; they may cause anxiety but may also be anxiolytic [39], etc. These observations are probably based on the control of these effects by several neuronal circuits influenced by cannabinoids. Recently, it has been demonstrated that signaling of the CB_1 receptor is profoundly altered by a

Table 1. Neurotransmitter Functions Under Cannabinoid Control

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

regulated association of CB_1 and dopamine-2 receptors [40]. The highest level of CB_1/D_2 receptor complexes was detected when both receptors were stimulated with sub-saturating concentrations of agonists. Concurrent receptor stimulation promoted a shift of CB_1 signaling from a pertussis toxin sensitive inhibition to a partly pertussis toxin insensitive stimulation of adenylate cyclase and phosphorylation by extracellular signal-regulated kinases 1 and 2 ($ERK_{1/2}$) [40]. A cross-talk between the CB_1 receptor and other receptors in the brain has also been reported for the corticotropin releasing hormone receptor type 1 ($CRHR_1$) in olfactory regions, in several cortical and limbic structures, and in some hypothalamic and thalamic nuclei [41] and for the μ-opioid receptor in the dorsal horn of the spinal cord [42].

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 [43], opioid receptor antagonists did not block the subjective effects of THC in humans in one study [44] or even increased the subjective effects THC in another study [45].

Not all compounds that activate cannabinoid receptors are cannabinoids. e.g. alkylamides of the Echinacea plant upregulated TNF-alpha mRNA, which was mediated by CB_2 receptors [46].

2.4. Additional Cannabinoid Receptors

Not all cannabinoid effects are mediated by CB receptors. The endocannabinoid 2-arachidonoyl glycerol suppressed interferon-gamma expression in splenocytes and there was no difference in magnitude of effect between cells derived from $CB_1(-/-)/CB_2(-/-)$ knockout mice and from controls [47]. The ability of cannabidiol to impair the migration of tumor cells was independent of CB_1 and CB_2 receptor activation [48]. The mechanisms of these effects are unknown. There is increasing evidence for the existence of additional cannabinoid receptor subtypes in the brain and periphery [49-51]. These receptors are more likely to be functionally related to the known cannabinoid receptors than have a similar structure, as there is no evidence for additional cannabinoid receptors in the human genome.

3. ENDOCANNABINOIDS

The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, endogenous cannabinoids or endocannabinoids [52-54]. All endocannabinoids are derivatives of arachidonic acid, thus differing in chemical structure from phytocannabinoids of the cannabis plant. To date, five endocannabinoids have been identified. These are *N*-arachidonoyl ethanolamide (AEA, anandamide) [52], 2-arachidonoyl glycerol (2-AG) [54, 55], 2-arachidonoyl glyceryl ether (noladin ether) [56], *O*-arachidonoyl ethanolamine (virodhamine) [57], and *N*-arachidonoyl-dopamine (NADA) [58]. The most important of these eicosanoid molecules are anandamide and 2-arachidonoyl glycerol (see Figs. **2** and **3**). Noladin ether was initially synthesized as a stable analog of 2-AG. Whether it is present in mammalian brain is controversial, since it was claimed to be an endocannabinoid by Hanus *et al.* (2001) [56], but could not be detected by another group in mammalian brains of several species, suggesting that it does not play a role in the central endocannabinoid system [59].

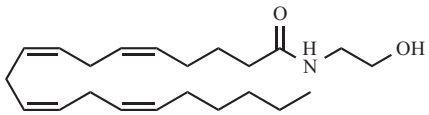

Fig. (2). Arachidonoyl ethanolamide (AEA, anandamide).

3.1. Binding to Cannabinoid and Vanilloid Receptors

When protected from enzymatic hydrolysis, anandamide has a similar affinity to the CB_1 receptor as Δ^9-THC [26]. Affinity to the CB_1 receptor is greater than CB_2 affinity. Anandamide behaves as a full agonist at the CB_1 receptor [60] and as a partial agonist at the CB_2 receptor. This means that anandamide elicits a lower maximal response than that of higher efficacy cannabinoid receptor agonists at the CB_2 receptor, possessing the mixed agonist-antagonist properties typical of partial agonists. In one experiment, anandamide was found to attenuate CB_2 receptor mediated responses to 2-AG, which was 3-fold more potent than anandamide [61].

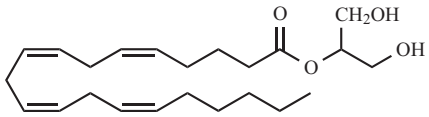

Fig. (3). 2-Arachidonoyl glycerol (2-AG).

Noladin ether and 2-AG are both cannabinoid receptor agonists, noladin ether having a much higher affinity for the CB_1 receptor than for the CB_2 receptor [26]. Virodhamine is a partial agonist with *in vivo* antagonist activity at the CB_1 receptor and full agonist activity at the CB_2 receptor [57]. NADA is an agonist at the CB_1 receptor [62].

Anandamide and NADA do not only bind to cannabinoid receptors but also share the ability of capsaicin, a constituent of hot chilli peppers, to stimulate vanilloid receptors (VR_1) [58, 62, 63]. The VR_1 is associated with hyperalgesia and may play a part in nociception. Since VR_1 is also widely distributed in the skin, it was recently proposed that this receptor does also play a central role in maturation and function of epithelial cells [64].

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". The potency and efficacy of anandamide at the vanilloid receptors is rather low. However, metabolites of anandamide may serve as endogenous ligands for these receptors [65]. NADA is a potent vasorelaxant, an effect mediated through VR_1 and CB receptors [66].

3.2. Production and Metabolism

The first two discovered endocannabinoids, anandamide and 2-AG, are best studied. They are synthesized in neuronal cells, including cortical and striatal neurons, but not astrocytes, and their synthesis is increased in response to membrane depolarization. Specific membrane depolarization-induced release is characteristic of classical neurotransmitters. However, in contrast to classical

neurotransmitters that are being synthesized and stored in intraneural vesicles, endocannabinoids are produced "on demand" by cleavage of membrane lipid precursors and released immediately from cells into the synapse in a stimulus-dependent manner [53]. The precursor of anandamide is N-arachidonoyl-phosphatidylethanolamine, which is hydrolyzed to the endocannabinoid by a phospholipase D-catalyzed process [67]. After release, endocannabinoids 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) and monoacylglycerol lipase [53, 68]. FAAH degrades anandamide to arachidonic acid and ethanolamide. In mice, lack of FAAH resulted in supersensitivity to anandamide and enhanced endogenous cannabinoid signaling [69]. Anandamide may also be converted to other metabolites by lipoxygenase or cyclooxygenase [26]. Other metabolic processes include acylation of noladin ether [70], oxidation of 2-AG and methylation of the aromatic moiety of NADA.

In all cases, cellular uptake must proceed metabolism since metabolism occurs only in the cells. Endocannabinoid uptake by cells seems to happen by "enhanced diffusion" through the cell membrane [57, 58, 71], even though an active carrier system has not been detected so far. Simple passive diffusion following a concentration gradient into the cells where they are quickly metabolized by FAAH, is regarded as unlikely, since several substances have been developed that are thought to inhibit anandamide cellular uptake without inhibiting FAAH, among them being Arvanil [72] and VDM11 [73], and noladin ether and NADA are rapidly taken up into cells even though they are rather stable or refractory to enzymatic hydrolysis [58, 70]. However, the discussion on the existence of a transport system is not finished, and one group demonstrated that Arvanil and other substances regarded as anandamide transport inhibitors (olvanil, AM404) were actually inhibitors of FAAH [74]. Intracellular uptake of endocannabinoids is a temperature dependent and rapid process with a half time of a few minutes, compared to hours in the case of exogenous plant cannabinoids.

As with the gene of the CB_1 receptor, there is interest in a possible contribution of variations of the gene encoding FAAH to the etiology of diseases. The sparse data on a possible link between drug abuse and dependence and a mutation of the FAAH gene and subsequent functional abnormalities in the endocannabinoid system are conflicting [75, 76]. A naturally occurring missense gene polymorphism (FAAH 385 A/A genotype) was reported to be associated with overweight and obesity [77].

3.3. Tonic Activity of the Cannabinoid System

When administered alone, cannabinoid receptor antagonists may behave as inverse agonists in several bioassay systems. In addition to blocking the effects of exogenous cannabinoidsm, they may also produce effects that are opposite in direction from those produced by cannabinoid receptor agonists, e.g. resulting in hyperalgesia [78], suggesting that the endogenous cannabinoid system is tonically active. Tonic activity may be due a constant release of endocannabinoids or from a portion of cannabinoid receptors that exist in a constitutively active state [27].

Tonic activity of the endocannabinoid system has been demonstrated in several conditions. Endocannabinoids have been shown to be tonically active in the dorsal horn neurons of the spinal cord, thus attenuating acute nociceptive transmission at the level of the spinal cord [79]. Endocannabinoid levels were increased in a pain circuit of the brain (periaqueductal gray) following painful stimuli [80]. 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 [73]. An increase of cannabinoid receptors following nerve damage was found in a rat model of chronic neuropathic pain [81] and in a mice model of intestinal inflammation [82]. 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 [83] and with regard to vomiting in emetic circuits of the brain [84]. Elevated endocannabinoid levels have been detected in cerebrospinal fluid of schizophrenic patients [85]. In other models, tonic or enhanced activity could not been demonstrated, e.g. in a rat model of inflammatory hyperalgesia [86].

4. MODULATORS OF THE ENDOCANNABINOID SYSTEM

Exogenous modulators of the endocannabinoid system comprise cannabinoid receptor agonists (cannabinoids), CB receptor antagonists and inhibitors of degradation and re-uptake of endocannabinoids that promote accumulation of endocannabinoids *in situ.* Antagonists have allowed a detailed investigation of mechanisms of cannabinoid actions and proved that not all cannabinoid effects were mediated by cannabinoid receptors, but that other mechanisms of action were involved. Both antagonists and agonist cannabinoids are under clinical investigation for a broad number of indications.

Cannabinoids were originally regarded as any of a class of *"typical C_{21} groups of compounds present in Cannabis sativa L."* [87]. The modern definition is termed with more emphasis on synthetic chemistry and on pharmacology, and encompasses kindred structures, or any other compound that affects cannabinoid receptors. This has created several chemical sub-categories that take into consideration the various forms of natural and synthetic compounds.

It has been proposed to use the term phytocannabinoid for the natural plant compounds [88] and endocannabinoids for the natural animal compounds [89], the endogenous ligands of the cannabinoid receptors. Synthetic agonists of these receptors have been classified according to their degree of kinship ("classical" *vs*. "non-classical") with phytocannabinoids.

4.1. Phytocannabinoids and their Metabolites

Natural plant cannabinoids are oxygen-containing aromatic hydrocarbons. In contrast to most other drugs, including opiates, cocaine, nicotine and caffeine, they do not contain nitrogen, and hence are not alkaloids.

Phytocannabinoids were originally thought to be only present in the cannabis plant (*Cannabis* sativa L.), but recently, some cannabinoid type bibenzyls have also been found in liverwort (*Radula* perrottetii and *Radula* marginata) [90], with the chemical structure of perrottetinenic acid in liverwort being similar to that of Δ^9-THC in cannabis.

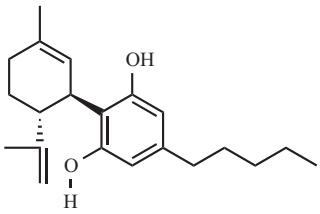

Fig. (4). Cannabidiol.

More than 60 cannabinoids have been detected in cannabis, mainly belonging to one of 10 subclasses or types [91], of which the cannabigerol type (CBG), the cannabichromene type (CBC), the cannabidiol type (CBD), the Δ^9-THC type, and the cannabinol type (CBN) are the most relevant in quantity. Cannabinoid distribution varies between different cannabis strains and usually only three or four cannabinoids are found in one plant in relevant concentrations. Δ^9-THC is largely responsible for the pharmacological effects of cannabis including its psychotropic properties, but other compounds of the cannabis plant are involved in these effects [92]. Concentrations of Δ^9-THC are below 0.2% in fiber-type cannabis varieties (hemp) used for the production of fiber and seeds, and may vary between 2 and 30% in the flowering tops and upper leaves in the female drug-type cannabis plant used for recreational and medicinal purposes.

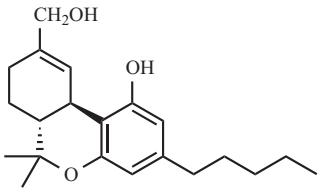

Fig. (5). 11-OH-THC (11-hydroxy-THC).

11-OH-Δ^9-tetrahydrocannabinol (11-OH-THC) is the most important psychotropic metabolite of Δ^9-THC with a similar spectrum of actions and similar kinetic profiles as the parent molecule [93, 94]. 11-nor-9-carboxy-THC (THC-COOH) is the most important non-psychotropic metabolite of Δ^9-THC.

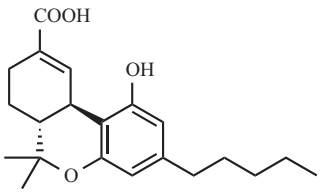

Fig. (6). THC-COOH (11-nor-9-carboxy-THC).

4.2. Synthetic Cannabinoids

According to their degree of kinship with the phytocannabinoids, synthetic cannabinoids may be described as classical or non-classical derivatives. Among the classical synthetic cannabinoids that retain the phytocannabinoid ring structures and their oxygen atoms are nabilone, nantradol, HU-210, and HU-211. Nabilone is available on prescription in several countries with a similar pharmacological profile as THC [95]. HU-210, an analog of Δ^8-THC with a dimethylheptyl side chain, is between 80 and 800 times more potent than THC [96, 97], while its enantiomer (mirror image) HU-211, is completely devoid of psychoactivity [98]. The latter, also called dexanabinol, is an NMDA antagonist with neuroprotective properties in hypoxia and ischemia [99]. CT3 or ajulemic acid, a derivative of the Δ^8-THC metabolite THC-COOH, is under clinical investigation for inflammation and pain [100].

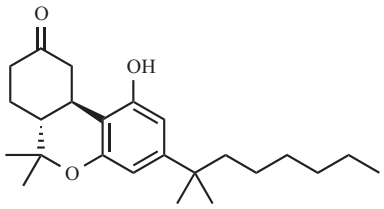

Fig. (7). Nabilone.

Levonantradol (Pfizer), a non-classical cannabinoid with a more radical deviation of the typical structure, was under clinical investigation for the treatment of pain [101] and the side effects of chemotherapy [102] and radiotherapy [103]. Other non-classical cannabinoids are the aminoalkylindol WIN-55,212-2, which has a 6.75-fold affinity towards the CB_2 receptor [104] and the bicyclic cannabinoid analog CP-55,940, a widely-used agonist for the testing of cannabinoid receptor affinity with potency 4-25 times greater than THC depending on assay [105].

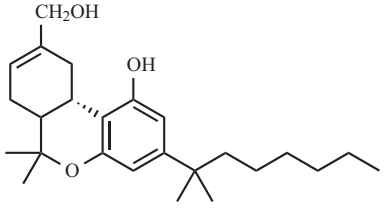

Fig. (8). Dexanabinol (HU211).

4.3. Endocannabinoid Analogs

Several anandamide congeners have been synthesized, among them is (*R*)-(+)-α-methanandamide that possesses both a four-fold higher affinity for the CB_1 receptor and a greater catabolic resistance than anandamide. Further anandamide analogs are arachidonoyl-2'-chloroethylamide (ACEA) and arachidonoyl cyclopropylamide (ACPA).

4.4. Inhibitors of Endocannabinoid Degradation

Fatty acid-based compounds have been synthesized that mimic the structure of anandamide, but act as inhibitors of membrane transport or of the catabolic enzyme FAAH [68]. The first of these compounds was N-(4-hydroxyphenyl) arachidonoylamide, usually designated as AM404. AM404 increases the plasma levels of anandamide in rats and causes a time-dependent decrease of motor activity, which is reversed by a cannabinoid CB_1 receptor antagonist [106]. It is unclear whether AM404 is a selective inhibitor of

anandamide transport or an inhibitor of FAAH [74]. It also activates vanilloid receptors and binds to CB_1 receptors, but it does not seem to be a CB_1 receptor agonist or antagonist [26]. Another inhibitor of membrane transport or FAAH is VDM-11, which also binds to CB_1 receptors.

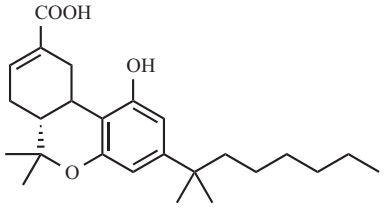

Fig. (9). CT3 (ajulemic acid, IP751).

A frequently used inhibitor of FAAH is phenylmethylsulfonyl fluoride (PMSF). The irreversible FAAH inhibitors palmitylsulphonoyl fluoride (AM374) and stearylsulphonoyl fluoride (AM381) are approximately 20 times more potent than PMSF in preventing the hydrolysis of anandamide in brain homogenates [107]. They both are only weak CB_1 receptor ligands [107]. Even more potent FAAH inhibitors have recently been developed [108].

4.5. Cannabinoid Receptor Antagonists

The first reported antagonist of a cannabinoid receptor binding site was announced by Rinaldi-Carmona *et al.* (1998) as the potent and orally-active CB_1-selective compound, SR141716A, that is also called rimonabant (Acomplia®) in clinical studies [109]. Rimonabant is a diarylpyrazole and the majority of CB_1 receptor antagonists can be regarded as a structural modification of this molecule [110]. A CB_2 selective antagonist synthesized by the same group at Sanofi-Synthelabo is SR144528. Both also bind to the other receptor type in higher concentrations. Further CB receptor antagonists with CB_1 selectivity are the diarylpyrazoles AM251 and AM281, and the substituted benzofuran LY320135. A CB_2 selective antagonist is the aminoalkylindole 6-iodopravadoline (AM630). Several pharmaceutical companies besides Sanofi-Synthelabo have patented CB receptor antagonists, among them being Pfizer, Bayer, Merck, Solvay Pharmaceuticals, Hoffmann-La Roche and AstraZeneca [110].

4.6. Affinity to the Cannabinoid Receptor

Both antagonists and CB receptor agonists show different affinity to CB_1 and CB_2 receptors. Synthetic cannabinoids have been developed that act as highly selective agonists at one of these receptor types [111, 27]. Several synthetic cannabinoid receptor agonists with significant selectivity for CB_2 receptors have a classical structure (L-759633, JWH-133, HU-308). The hydroxy group of THC has been replaced by a methoxy group or removed in these molecules. A potentially important class of CB_1 receptor selective agonists are anandamide analogs, including (*R*)-(+)-α-methanandamide, ACEA and ACPA.

Δ^9-THC has approximately equal affinity for the CB_1 and CB_2 receptor, while anandamide has marginal selectivity for CB_1 receptors [111]. However, the efficacy of THC and anandamide is less at CB_2 than at CB_1 receptors.

The affinity to CB receptors and the pharmacological activity of Δ9-THC is stereoselective, with the natural (-)-*trans* isomer (dronabinol) being 6-100 times more potent than the (+)-*trans* isomer depending on the assay [113]. Not all phytocannabinoids are agonists to the cannabinoid receptor. The mechanism of action and the pharmacology of CBD considerably differ from that of THC. As with THC and other phytocannabinoids, the natural CBD is a (-)-enantiomer. However, in contrast to (-)-Δ9-THC, (-)-cannabidiol does not have a significant affinity to cannabinoid receptors, while its synthetic (+)-enantiomer does [114].

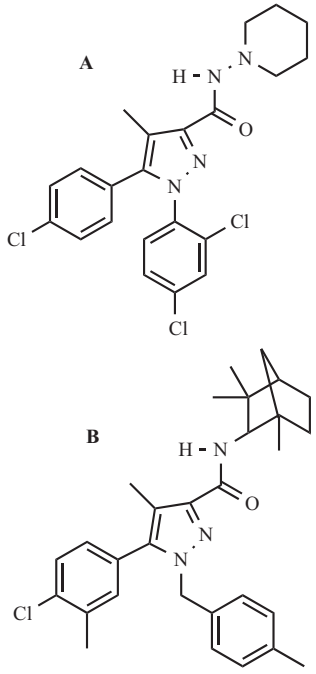

Fig. (10). Cannabinoid receptor antagonists, SR 141716A (A), a selective CB_1 receptor antagonist,and SR 144528 (B), a selective CB_2 receptor antagonist.

5. PHARMACOLOGY

The best-studied modulator of the endocannabinoid system is the phytocannabinoid and CB receptor agonist Δ^9-THC. While THC is still favored in clinical studies; basic research is often conducted with more potent CB receptor agonists, such as WIN55,212-2, HU-210 and CP-55,940.

5.1. Δ^9-THC and Other CB Receptor Agonists

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 [115], some neuroprotective effects [116], and anti-emetic effects. The anti-emetic effects of THC are reported to be in part mediated by CB_1 receptors [117] and in part by non-CB mechanisms; the rationale for the clinical use of THC as an anti-emetic in children receiving cancer chemotherapy [118]. Due to the lower CB_1 receptor density in the brain of children compared with adults, they tolerated relatively high

doses of Δ^8-THC in a clinical study, without significant CB_1 receptor mediated adverse effects [118]. In a study with cells stably transfected with the human 5-HT_{3A} receptor, several (endo)cannabinoids (THC, WIN55,212-2, anandamide, etc.) directly inhibited currents induced by 5-hydroxytryptamine [119]. Since 5-HT_3 antagonists are potent anti-emetic drugs, this may be one mechanisms by which cannabinoids act as anti-emetics.

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

The activation of the cannabinoid system *via* phytocannabinoids such as THC, and synthetic and endogenous cannabinoids causes numerous actions that have been extensively reviewed [113, 120-128]. 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 [129].

Psyche, Cognition and Behavior

In many species, the behavioral actions of low doses of THC are characterized by a unique mixture of depressant and stimulant effects in the CNS [113]. 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 [35]. It may induce sleep [130, 131].

Acute THC intoxication impairs learning and memory [132-134], and adversely affects psychomotor and cognitive performance [135], reducing the ability to drive a car and to operate machinery. Reduced reaction time also affects the iris constriction response of the eye. A brief light flash shows decreased amplitude of constriction and a decelerated velocity of constriction and dilation [136]. Tolerance may develop to the impairment of psychomotor and cognitive performance with long-term use. In a study that compared information processing in heavy cannabis users with non-users there was no difference when users were under the influence of the drug, while there were significantly slowed information-processing speeds in the subacute phase in the cannabis users, which may be attributed to withdrawal [137].

The most conspicuous psychological effects of THC in humans have been divided into four groups: affective (euphoria and easy laughter), sensory (increased perception of external stimuli and of the person's own body), somatic (feeling of the body floating or sinking in the bed), and cognitive (distortion of time perception, memory lapses, difficulty in concentration) [138].

These effects only appear if an individually variable threshold of dose is exceeded. During a study on the efficacy of dronabinol (THC) in 24 patients with Tourette's 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) [139].

Stress, Anxiety and Fear

The endocannabinoid system may serve as a novel approach to the treatment of anxiety-related disorders. Endocannabinoid signaling negatively modulates the function of the hypothalamic-pituitary-adrenal axis in a context-dependent manner [140]. Upon exposure of mice to acute stress, hypothalamic 2-arachidonoyl glycerol content was reduced compared with the control value; however, after 5 days of stress, which resulted in an attenuated corticosterone response, the hypothalamic 2-AG content was increased compared with the control value. The CB_1 receptor agonist CP55940 reduced blood corticosterone levels in stressed mice, while a CB_1 receptor antagonist increased corticosterone concentrations [140]. A similar effect was achieved by the administration of the putative endocannabinoid transport inhibitor AM404, or the FAAH inhibitor URB597. Another group observed reduced hippocampal 2-AG levels following chronic stress [141]. Chronic stress impaired reversal learning and induced perseveratory behavior in the Morris water maze, an impairment that was reversed by exogenous cannabinoid administration, suggesting deficient endocannabinoid signaling. Data on the effects of cannabinoids on stress are conflicting. In humans, cannabis may cause anxiety and panic, reactions that may be potentiated by stress. Animal research demonstrated that there may be a synergistic interaction between stress and CB_1 receptor agonists (THC, CP55940) in the effects on amygdalar activity [142].

CB_1-deficient mice showed strongly impaired short-term and long-term extinction of aversive memories [143], and blockade of the CB_1 receptor in rats led to a dose-dependent decrease in extinction of conditioned fear [144]. These effects may explain the anxiety reducing effects in posttraumatic stress disorder and similar conditions. However, in contrast to AM404, which enhanced the extinction of conditioned fear, the administration of the CB_1 agonist WIN 55,212-2 did not appear to affect extinction [144].

Neuroprotection

One important physiological role of endocannabinoids seems to be neuroprotection [145]. Ischemia and hypoxia in the CNS induce abnormal glutamate hyperactivity and other processes that cause neuronal damage. These processes also play a role in chronic neurodegenerative diseases such as Parkinson's and Alzheimer's disease and multiple sclerosis. Neuroprotective mediators are also released in ischemia and hypoxia, including anandamide and 2-AG. When these two endocannabinoids were administered after traumatic brain injury in animals, they reduced brain damage [145]. Neuroprotective cannabinoid mechanisms observed in animal studies include reduction of glutamate toxicity by inhibition of excessive glutamate production, inhibition of calcium influx into cells, anti-oxidant properties which reduce damage caused by oxygen radicals and modulation of vascular tone [99, 116, 146]. Cannabinoids reduce brain inflammation. The CB agonist WIN55,212-2 reduced the production of several key inflammatory mediators by activated human astrocytes, including NO (nitric oxide),

TNF-alpha (tumor necrosis factor alpha), and several chemokines [147]. CB_1 receptors seem to play a major role in neuroprotection by endocannabinoids, since CB_1(-/-) mice showed little spontaneous recovery after closed head injury compared to controls [148]. Receptor-stimulated inhibition of protein kinase A was reported to be required for the neuroprotective effects of CB_1 receptor activation [149].

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 [150]. CB_1 and CB_2 receptor agonists reduce amyloid-beta toxicity *in vitro* and *in vivo* [151, 152]. Enhanced amyloid-beta peptide deposition along with glia cell activation in senile plaques plays a major role in the pathology of Alzheimer's disease (AD). CB_1 positive neurons are greatly reduced in areas of microglial activation, and CB_1 receptor protein expression is markedly decreased in AD brains [152]. Amyloid-beta induced activation of microglial cells, cognitive impairment and loss of neuronal markers was prevented by cannabinoids in rats [152].

Circulatory System

THC can induce tachycardia [138] and increase cardiac output with increased cardiac labor and oxygen demand [153]. It can also produce peripheral vasodilation, orthostatic hypotension [125, 154] and reduced platelet aggregation [155]. Data on cerebral blood flow effects are contradictory. Regional increases and decreases of blood flow with no mean change of flow were reported by one group [156], while a recent report suggests that systolic velocity and the pulsatility index, a measure of cerebrovascular resistance, were significantly increased in cannabis users [157]. These effects persisted in heavy users for more than one month of monitored abstinence and were regarded as a partial explanation for cognitive deficits in heavy cannabis users.

In young healthy subjects, the heart is under control of the vagus that mediates bradycardia. Tachycardia by THC may easily be explained by vagal inhibition (inhibited release of acetylcholine) through presynaptic CB_1 receptors [158], which can be attenuated by beta-blockers [138] and blocked by the selective CB_1 antagonist SR141716A [159]. Regular use can lead to bradycardia [154]. The endocannabinoid system plays an important role in the control of blood pressure. Hypotension is mediated by central inhibition of the sympathetic nervous system, apparently by activation of CB_1 receptors, since this effect can also be prevented by a CB_1 antagonist [160]. Endocannabinoids are produced by the vascular endothelium, circulating macrophages and platelets [161]. Vascular resistance in the coronaries and the brain is lowered primarily by direct activation of vascular cannabinoid CB_1 receptors [162].

Appetite, Eating and Digestion

The endogenous cannabinoid system plays a critical role in milk ingestion of new-born mice [50]. Blockade of the CB_1 receptor results in death of new-borns [163]. Anandamide induces over-eating in rats through a CB_1 receptor mediated mechanism [164]. Endocannabinoids in the hypothalamus are part of the brain's complex system for controlling appetite including a significant component that is regulated by leptin [83]. Leptin is a major signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. Leptin reduces food intake by upregulating appetite-reducing neuropeptides, such as alpha-melanocyte-stimulating hormone, and downregulating appetite-stimulating factors, primarily neuropeptide Y. In animal research, reduced levels of leptin were associated with elevated levels of endocannabinoids in the hypothalamus, and application of leptin reduced endocannabinoid levels [83]. Cannabinoid-induced eating is ascribed to an increase of the incentive value of food [165].

Cannabinoid agonists inhibit gastrointestinal motility and gastric emptying in rats [166]. In a study with humans, THC caused a significant delay in gastric emptying [167]. In addition, CB agonists inhibited pentagastrin-induced gastric acid secretion in the rat [168], mediated by suppression of vagal drive to the stomach through activation of peripheral CB_1 receptors [169, 170].

Immune System

Animal and cell experiments have demonstrated that THC exerts complex effects on cellular and humoral immunity [171, 172]. It is not clear; to what extent these effects are of clinical relevance in humans with respect to beneficial (inflammation [173, 174], allergies [175], autoimmune processes [172]) and undesirable effects (decreased resistance towards pathogens and carcinogens) [171]. THC was shown to modulate the immune response of T lymphocytes [176]. It suppressed the proliferation of T cells and changed the balance of T helper 1 (Th_1) and T helper 2 (Th_2) cytokines. It decreased the pro-inflammatory Th_1 reaction (e.g. the production of interferon-gamma) and increased the Th_2 reaction. This may explain why THC is effective against inflammation with a strong Th_1 reaction, e.g. in multiple sclerosis, Crohn's disease and arthritis. The regulation of the activation and balance of human Th_1/Th_2 cells seems to be mediated by a CB_2 receptor-dependent pathway [176].

Additional Organ Systems and Effects

Antiviral actions. Incubation with THC reduced the infectious potency of herpes simplex viruses [177]. Micromolar concentrations of THC inhibit Kaposi's Sarcoma Associated Herpes virus and Epstein-Barr virus reactivation in virus infected B cells [178].

THC also strongly inhibited lytic replication of several oncogenic viruses *in vitro* [178].

Bones and cartilage. Preliminary observations presented by Mechoulam *et al*. in 2003 at the First European Workshop on Cannabinoid Research in Madrid, Spain, show that endocannabinoids seem to stimulate bone formation. During differentiation, osteoblast precursor cells have progressively increased levels of CB_2 but not of CB_1 as measured by reverse transcription polymerase chain reaction. In addition, normal mice treated systematically with 2-AG showed a dose dependent increase in trabecular bone formation. The peptide leptin is not only known to negatively regulate endocannabinoid activity in appetite

control, but also to influence osteoblastic activity. Results of experimental research by another group suggest that some cannabinoids may prevent cartilage resorption, in part, by inhibiting proteoglycan degradation and also by inhibiting cytokine production of chondrocytes induced by the free radical nitric oxide (NO) [179].

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 [180]. Vasodilation in the eye is observed as conjunctival reddening after THC exposure [113]. THC and some other cannabinoids decrease intraocular pressure [180, 181]. CB_1 receptors in the eye are involved in this effect, while CB_2 receptor agonists do not reduce intraocular pressure [182].

Genetic and cell metabolism. THC can inhibit DNA, RNA, and protein synthesis, and can influence the cell cycle. However, very high doses are required to produce this effect *in vitro* [183]. Cannabinoid agonists inhibited human breast cancer cell proliferation *in vitro* [184, 185], and, directly applied at the tumor site, showed antineoplastic activity against malignant gliomas in rats [186].

Hormonal system and fertility. THC interacts with the hypothalamic-pituitary adrenal axis influencing numerous hormonal processes [187]. Minor changes in human hormone levels due to acute cannabis or THC ingestion usually remain in the normal range [125]. Tolerance develops to these effects, however, and even regular cannabis users demonstrate normal hormone levels.

Pregnancy. Anandamide levels during pregnancy show a characteristic pattern [188]. Mean plasma levels were 0.9 nm in the first trimester and 0.4 nm in the second and third trimester. During labor, anandamide plasma levels rose to 2.5 nm. Postmenopausal and luteal-phase levels were similar to those in the first trimester. It is currently unclear whether implantation of the embryo can be disrupted by THC.

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 [189]. In animal studies high doses of cannabinoids inhibited the acrosome reaction [190].

5.2. Endocannabinoids and Inhibitors of Endocannabinoid Degradation

Several similarities have been described between exogenous cannabinoid receptor agonists and endocannabinoids, with regard to their pharmacology and medicinal effects [26]. Inhibitors of endocannabinoid degradation may be promising candidates for therapeutic modulation of the endocannabinoid system.

FAAH inhibitors produced analgesia in animal models [191] and AM404 reduced the expression of c-fos, a marker of activated neurons in an experimental model of neuropathic pain [192]. In the latter study, both CB_1 and CB_2 receptors as well as vanilloid receptors were involved in the observed effect. Another group demonstrated that blockers of anandamide hydrolysis were able to reduce anxiety in animal tests [193]. These benzodiazepine-like properties were accompanied by augmented brain levels of anandamide and were prevented by CB_1 receptor blockade. Recently, it has been shown that two selective inhibitors of the putative endocannabinoid transporter and hence of endocannabinoid inactivation, provide an effective therapy for Theiler murine encephalomyelitis, a virus-induced demyelinating disease and an animal model of multiple sclerosis [194]. Treatment of infected mice with the transport inhibitors OMDM1 and OMDM2 enhanced anandamide levels in the spinal cord, ameliorated motor symptoms and decreased inflammatory responses. This effect resembles that of exogenous cannabinoid receptor agonists [195].

However, there are several differences in the pharmacology of exogenous cannabinoids and endocannabinoids [196]. An animal study found cross-tolerance between THC and anandamide for antinociception, but not for suppression of spontaneous activity, catalepsy and hypothermia in mice tolerant to THC [196]. These results suggest that the pharmacology of anandamide only partially overlaps with that of THC and other exogenous cannabinoids.

Some non CB effects of anandamide may be mediated by vanilloid receptors. For example, inhibition of cell proliferation of rat C6 glioma cells by endocannabinoids was reported to involve combined activation of both vanilloid receptors and to lesser extent, cannabinoid receptors [197]. The vasodilation caused by anandamide in the splanchnic arteries was also reported to be mediated by both CB_1 and vanilloid receptors [198].

While anandamide and 2-AG have similar affinities to the CB_1 and to the CB_2 receptor, there seem to be differences in their pharmacology. 2-arachidonoyl glycerol was shown to induce the migration of natural killer cells, which was abolished by treatment with a CB_2 receptor antagonist (SR144528) [199]. In contrast to 2-AG, anandamide and THC did not induce the migration. In fact, the combined application of THC and 2-AG abolished the migration induced by the latter [199]. Experiments with rat hippocampal slices provide another example for differences in the effects of anandamide and 2-AG [63]. While 2-AG reduced paired-pulse depression of population spikes mediated by CB_1 receptors, anandamide increased paired-pulse depression by acting on hippocampal vanilloid receptors.

5.3. Cannabidiol

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 [200]. In a study by Petitet *et al.* (1998) [201], CBD considerably reduced the receptor activation by the potent classical CB_1 receptor agonist CP55940. (2) CBD stimulates the vanilloid receptor type 1 with a maximum effect similar in efficacy to that of capsaicin [202]. (3) CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide, thus increasing its concentration [202, 203]. (4) Finally, CBD may also increase the plasma THC level [204] by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system [205, 206]. However, there was no or minimal effect of CBD on plasma levels of THC in man [207, 208].

In a study that analyzed the mode of action of the anti-inflammatory and anti-hyperalgesic effects of CBD, simultaneous administration of a VR_1 receptor antagonist fully reversed the anti-hyperalgesic effects [209]. A CB_2 receptor antagonist was partly effective and a CB_1 receptor antagonist had no effect. The anti-inflammatory efficacy of CBD was unrelated to cyclooxygenase (COX) activity, but CBD inhibited the endothelial isoform of nitric oxide synthase (eNOS). In a rat model of arthritis, low doses of CBD decreased prostaglandin E_2, nitric oxide and lipid peroxide level, mediators that are all known to be involved in the development and maintenance of arthritis [209].

CBD exerts sedating [210], anti-epileptic [211], anti-dystonic [212], anti-emetic [213], and anti-inflammatory [214, 215] effects. It reduced intraocular pressure [216], was neuroprotective [116], and antagonized the psychotropic and several other effects of THC [200].

5.4. THC Metabolites and Derivatives

After intravenous administration in humans, 11-OH-THC was equipotent to THC in causing psychic effects and reduction in intraocular pressure [94]. In some pharmacological animal tests, 11-OH-THC was 3 to 7 times more potent than THC [217].

THC-COOH possesses anti-inflammatory and analgesic properties by mechanisms similar to non-steroidal anti-inflammatory drugs (NSAIDs) [218-220]. Typical properties of NSAIDs apparently not shared by THC-11-oic acid are the major adverse effects of NSAIDs, namely, gastrointestinal and kidney toxicity [100]. The precise basis for this difference is not well-understood; however, it may be partly due to a selective inhibition by THC-11 oic acid for COX-2 vs COX-1 (cyclooxygenase). THC-COOH antagonizes some effects of the parent drug through an unknown mechanism, e.g. the cataleptic effect in mice [221]. Ajulemic acid (CT3), a synthetic derivative of THC-COOH, shows a similar pharmacological profile as the natural substance. Recently, a possible mechanism of action was proposed for this derivative [222]. Ajulemic acid binds directly and specifically to the peroxisome proliferator-activated receptor gamma (PPARgamma), a pharmacologically important member of the nuclear receptor superfamily. In addition, it was shown that ajulemic acid inhibited interleukin-8 promoter activity in a PPARgamma-dependent manner, suggesting a link between the anti-inflammatory action of the cannabinoid acid and the activation of PPARgamma. Additionally, CT3 binds to CB_1 and CB_2 receptors, but has a more limited brain access and is somewhat better tolerated than THC [223].

5.5. Antagonists

SR141716A was able to block the psychological and physiological effects of THC in humans in a dose-dependent manner [159]. Three mechanisms are proposed to account for inverse cannabimimetic effects of antagonists, (1) antagonism of endocannabinoids, (2) modulation of CB_1 receptors, possibly through an allosteric mechanism shifting them from a constitutively active state to an inactive state, (3) CB_1 receptor-independent mechanisms, for example antagonism at A_1 receptors of endogenous adenosine [224]. Experiments with mice lacking CB_1 receptors (CB_1-/- mice) or with tissues from CB_1-/- mice suggest that rimonabant (SR141716A) produces at least some of its effects by binding to CB_1 receptors. CB1 receptor knockout mice eat less than their wild-type littermates [83]. SR141716A has been found to reduce food intake in CB_1+/+ mice but not in CB_1-/- mice [224].

Reviews of the pharmacological effects of cannabinoid receptor antagonists are presented by Pertwee (2005) and Lange and Kruse (2004) [110, 224]. Among the effects of CB_1 antagonists reported are increased locomotor activity in rats and mice, improvement of memory in rats and mice, increased nociception (inflammatory and neuropathic pain or allodynia) in rats and mice, evocation of emesis in shrews, spasticity and tremor in a mouse model of multiple sclerosis, accelerated intestinal transit in rats and mice, increase of severity of induced colitis in mice, and decrease of milk-ingestion and growth in mouse pups. Schlicker and Kathmann (2001) reviewed the inverse cannabimimetic effects of SR141716A on neurotransmitter release *in vitro*, among them being the evocation of acetylcholine release, noradrenaline release, GABA release, dopamine release, glutamate release, and D-aspartate release in several brain tissues in rats, mice and guinea-pigs [225].

The effects of physiological or increased endocannabinoid levels may be reduced by the application of CB antagonists as proven in several animal models. Rimonabant may produce hyperalgesia due to the blockade of endocannabinoid effects [80]. Increased anandamide and 2-arachidonoyl glycerol levels are observed in basolateral amygdala complex of auditory fear-conditioned mice. Endocannabinoids are thought to promote extinction of aversive memories in these animals, a process that was impaired by the application of rimonabant [143]. Endocannabinoid concentrations are also elevated in the brain and spinal cord of spastic mice with chronic relapsing experimental allergic encephalomyelitis (CREAE). Spasticity in these animals may be exacerbated by the CB_1 receptor antagonist [73].

6. THERAPEUTIC POTENTIAL

Cannabis preparations and single cannabinoids have been employed in the treatment of numerous diseases [123, 126, 127, 226]. Besides phytocannabinoids, several synthetic cannabinoid derivatives are under clinical investigation that are devoid of psychotropic effects or have fewer side effects. Antagonists at the CB_1 receptor have followed and inhibitors of endocannabinoid degradation will presumably follow.

6.1. Cannabinoid Receptor Agonists

Clinical studies with single cannabinoids and whole plant preparations (smoked cannabis, encapsulated cannabis extract, sublingual liquid preparations) have often been inspired by anecdotal experiences of patients employing crude cannabis products. The anti-emetic [227], and the appetite enhancing effects [228], muscle relaxation [229], analgesia [230], and therapeutic use in Tourette's syndrome [231] were all discovered or re-discovered in this manner.

Incidental observations have also revealed therapeutically useful effects. This occurred in a study of Volicer *et al.* (1997) in patients with Alzheimer's disease, wherein the primary issue was an examination of the appetite-stimulating effects of Δ^9-THC [232]. Not only appetite and body weight increased, but disturbed behavior among the patients also decreased following the intake of the drug. The discovery of decreased intraocular pressure with THC administration in the beginning of the 1970s was also serendipitous [233], when several research groups screened for effects of cannabis on the human body. The investigation of anti-cancer effects of THC and other cannabinoids was stimulated by a long-term animal study in rats and mice that studied possible cancer causing actions of THC [234].

Several surveys have shown that cannabis is self-administered to treat a broad range of chronic illnesses. The largest of these investigations with 2969 returned questionnaires conducted in the United Kingdom revealed that cannabis was used by a considerable percentage of patients, in chronic pain (25%), multiple sclerosis (22%), depression (22%), arthritis (21%) and neuropathy (19%) [235]. Sixty-eight per cent said cannabis considerably eased their symptoms. Another survey among 252 HIV patients, of whom 175 (69%) were on antiretroviral therapy (ART) found that those who suffered from nausea were about three times more likely to adhere to ART if they used cannabis compared to non-users [236].

Several states of the United States allow the medical use of cannabis and some of them have established an identification card system. In Oregon, about 10,000 subjects are registered card-holders with recommendations by about 1,500 physicians (http://www.dhs.state.or.us/publichealth /mm/data.cfm). Since September 2003, cannabis is available in Dutch pharmacies, distributed by the Office of Medicinal Cannabis of the Health Ministry. In Canada, patients may apply to the Health Ministry for a legal use of cannabis on the basis of recommendations by their physicians.

Besides THC (Marinol™, Solvay Pharmaceuticals), several whole cannabis plant preparations are currently under clinical investigation, including Cannador™ of the Institute for Clinical Research in Berlin, Germany, a capsulated cannabis extract, and Sativex™ of the British company GW Pharmaceuticals, an under the tongue spray. Cannador and Sativex are both standardized on THC and CBD content, Sativex containing equal amounts of the two cannabinoids and Cannador containing more THC than CBD. At the Center for Medicinal Cannabis Research at the University of California, the therapeutic potential of smoked cannabis and inhaled cannabis by means of a vaporizer are investigated.

Hierarchy of Therapeutic Effects

Possible indications for cannabis preparations have been extensively reviewed [123, 126, 127, 226, 237-240]. To do justice to the scientific evidence with regard to different indications, a hierarchy of therapeutic effects can be devised, with established effects, effects with clinical and preclinical confirmation and effects based on preclinical, mechanistic studies. However the history of research into the therapeutic benefits of cannabis and cannabinoids has demonstrated that the scientific evidence for a specific indication does not necessarily reflect the actual therapeutic potential for a given disease.

Established Effects

Δ^9-THC (dronabinol, Marinol) is approved in several countries for medicinal use in refractory nausea and vomiting caused by antineoplastic drugs used for the treatment of cancer (for review see: [112]) and for appetite loss in anorexia and cachexia of HIV/AIDS patients [228, 241, 242]. These effects can be regarded as established effects for THC and cannabis. Nabilone (Cesamet™) is the second cannabinoid available on prescription, against nausea and vomiting associated with cancer chemotherapy.

In more than 30 studies, THC and nabilone have been shown to have a similar anti-emetic efficacy as the phenothiazines [112]. In the 1980s, several clinical studies with smoked cannabis have been performed in the USA, in which smoked cannabis was effective similar as THC (for review see: Musty & Rossi 2001). In the Lynn Pierson Research Program of New Mexico, 256 subjects who underwent chemotherapy received either THC or smoked cannabis, both drugs reduced nausea from 4.5 to 2.0 on average on a scale between 1 (no problem) and 5 (severe) and emesis from 4.3 to 1.7 on average [243]. There are no clinical studies comparing cannabinoids and 5-HT_3 (serotonin) antagonists, but a study with healthy subjects showed that ondansetron was significantly more effective than smoked cannabis [244]. Nausea and emesis were induced by syrup of ipecac. Cannabis significantly reduced ratings of nausea and slightly reduced the incidence of vomiting compared to placebo, while ondansetron completely eliminated the emetic effects of ipecac. In a clinical setting, 5-HT_3 antagonists are usually superior to THC, but the cannabinoid has proven to be effective at least in some cases of intractable nausea and vomiting [245]. Animal research demonstrated that THC reinforces the anti-emetic effects of ondansetron in vomiting produced by cisplatin [246], suggesting that a combination of both drugs may be meaningful in clinical practice.

THC is effective in AIDS wasting and cancer cachexia [247]. THC (2 x 2.5 mg) was less effective than megestrol acetate (800 mg daily). However, in these and some other studies, THC or cannabis may have been underdosed. It appears that 10 to 20 mg of THC are necessary for the treatment of weight loss [248]. In HIV-patients with significant loss of muscle mass, oral THC (10, 20 and 30 mg) and smoked cannabis (1.8, 2.8 and 3.9% THC) caused a significantly increased caloric intake compared to controls (HIV-patients without weight loss), but the highest THC dose was not well-tolerated.

Neuropathic pain seems to be the next indication, which can be regarded as established for a treatment with cannabis-based medicines. In 2005 Sativex received approval by Health Canada for relief of neuropathic pain in multiple sclerosis. Several case reports and small clinical studies indicate that THC and cannabis may be effective in treating several conditions of chronic pain [249-252, 254, 255]. A review of 2001 concluded that cannabinoids are no more effective than codeine in controlling chronic pain [256], and a commentary noted that cannabinoids may have potential in treating neuropathic pains, particularly those with spastic

components [257]. A therapeutic potential in neuropathic pain is supported by experimental data on anti-hyperalgesic properties of cannabinoid receptor agonists [258]. Later and studies with a larger patient population confirmed this assumption. Berman *et al.* (2004) observed a significant decrease in pain and improved sleep by two different cannabis extracts in 48 patients with neuropathic pain from brachial plexus avulsion [259]. In addition, there are several reports of pain reduction in multiple sclerosis by THC [260, 261] and cannabis [261, 262]. One recent study observed significant analgesic effects of THC and Sativex in chronic pain of different origins (multiple sclerosis, spinal cord injury, brachial plexus avulsion, stiff-man syndrome, etc.) [263]. In contrast to these studies, Attal *et al.* (2004) only found a therapeutic effect of oral THC in one of seven patients with chronic refractory neuropathic pain [264].

Cannabinoid receptor agonists and opiates were shown to act synergistically in animal models of pain [265-267], a rationale for the observation of additive effects of THC and morphine in pain therapy.

Effects with Clinical and Preclinical Confirmation

Several small studies in the 1980s and 1990s investigated the therapeutic potential of THC, cannabis and nabilone in spasticity due to spinal cord injury [25, 255, 268] and multiple sclerosis [255, 268- 272]. This indication is another target of current interest for cannabis-based drugs [38, 261 273-277]. Spasticity is difficult to treat with available drugs, as reviewed by Shakespeare *et al.* (2000) [278]. Only intrathecal application of baclofen resulted in a significant improvement in spasticity scores according to the Ashworth Scale and activities of daily living (ADL). Tizanidine resulted in improved spasticity but did not improve ADL, and side effects (sleepiness, dry mouth).

Recent larger placebo controlled trials for the investigation of the efficacy of cannabis and THC in spasticity were restricted to multiple sclerosis patients [261, 273, 275-277], and there is only one small study on cannabinoids in spasticity due to spinal cord injury conducted in the past few years [38]. Killestein *et al.* (2002) were unable to find any benefits of THC and Cannador in multiple sclerosis patients with severe spasticity, but doses applied (2 x 2.5 mg or 2 x 5 mg THC) were probably too low to get the desired therapeutic effects [274]. Other studies generally indicate significant effects in subjective ratings, and not in objective spasticity scores [261, 275, 276]. Preliminary results of a first long term study of THC and Cannador in multiple sclerosis suggest that THC may have long-term beneficial effects on the course of the disease. Results of the short-term trial (15 weeks) with eligible 630 patients are conflicting [408]. Eighty per cent of the original study population participated in a 12 months follow-up study. In the 15-week study, 657 patients with stable multiple sclerosis and muscle spasticity received a maximum daily dose of 10-25 mg THC as single agent or in a cannabis extract. There was no significant effect of cannabinoids on objective spasticity scores according to the Ashworth scale, but patients reported subjective improvements in pain and spasticity. In the long-term study, there was a significant improvement of spasticity scores in the THC group.

Cannabinoids may also be effective in some other movement disorders, including Tourette's syndrome, dystonia and levodopa-induced dyskinesia [17, 229, 279-283]. Results were conflicting in two small clinical trials on cannabinoids in levodopa-induced dyskinesia in Parkinson's disease. While a study with nabilone (n=7) significantly improved dyskinesia [284], a cannabis extract was ineffective in another investigation (n=19) [285].

In 1971, during a systematic investigation of its effects in healthy cannabis users, cannabis reduced intraocular pressure, suggesting a therapeutic potential in glaucoma. In the following 12 years, a number of studies in healthy individuals and glaucoma patients with cannabis and several natural and synthetic cannabinoids were conducted [233, 286-289]. Cannabis decreased intraocular pressure by an average 25-30%, occasionally up to 50%, the effect lasting 4-6 h. Neuroprotective benefits of cannabinoids may be of additional value in preventing damage to the optical nerve [180].

Experiments examining the anti-asthmatic effect of THC or cannabis in healthy and asthmatic subjects date mainly from the 1970s, and are all acute studies [290-292]. The effects of a cannabis cigarette (2% THC) or oral THC (15 mg), respectively, approximately correspond to those obtained with therapeutic doses of common bronchodilator drugs (salbutamol, isoprenaline). Experimental research suggests that cannabinoid receptor agonists possess further properties that may be of value in asthma. They inhibited capsaicin-induced bronchial smooth muscle contraction and reduced inflammation of the respiratory tract by blocking the release of the inflammatory cytokine tachykinin [293]. Several phytocannabinoids possess an anti-allergic potential. THC and cannabinol attenuated the increase of the interleukins IL-2, IL-4, IL-5, and IL-13 in reaction to sensitization with ovalbumin in mice. In addition, the elevation of serum IgE and the mucus overproduction induced by ovalbumin was markedly attenuated by the two cannabinoids [175].

A few studies investigated anxiolytic properties of nabilone [39, 294, 295]. In one of these investigations, 25 outpatients suffering from anxiety received either placebo or nabilone over a 28-day treatment period [39]. Those treated with the verum showed a dramatic improvement in anxiety.

THC was shown to reduce agitation in patients with Alzheimer's disease. Results of a small placebo controlled trial [232] were confirmed by Ross and Shua-Haim in a phase II open label parallel-group study involving 54 patients. The latter findings were presented at the American Society of Consultant Pharmacists' annual meeting in November 2003. Evaluation at nine weeks of treatment with 2 x 2.5 or 2 x 5 mg THC found significant reductions of agitation scores in both groups. There also was a trend towards a decrease in the caregiver burden scores.

In addition to the indications, above, there are several indications, in which benefits are generally implied in case reports. These include allergies [296], inflammation [127], epilepsy [297], intractable hiccups [298], depression [241], bipolar disorders [299], dependency to opiates and alcohol [296, 300,], withdrawal symptoms [300], and post-traumatic

stress disorder [127]. A first clinical study on THC in post-traumatic stress disorder of Israeli soldiers is currently under way.

Preclinical, Mechanistic Studies

Basic research shows promising possible future therapeutic uses, among them being neuroprotection in hypoxia and ischemia [99, 116]. Some immunological mechanisms of THC hint to possible benefits in autoimmune diseases, such as multiple sclerosis, arthritis, and Crohn's disease [172]. In a murine model of multiple sclerosis, cannabinoids significantly improved the neurological deficits in a long-lasting way. On a histological level, they reduced microglial activation and decreased the number of CD4+ infiltrating T cells in the spinal cord [301]. Another group found that amelioration of clinical disease in the same multiple sclerosis model was associated with downregulation of myelin epitope-specific Th_1 effector functions (delayed-type hypersensitivity and IFN-gamma production) and the inhibition of the proinflammatory cytokines, TNF-alpha, interleukin 1-beta, and interleukin-6 [302]. Raman *et al.* (2004) reported that treatment with THC was effective in a mouse model of amyotrophic lateral sclerosis if administered either before or after onset of disease signs, which they attributed to the reduction of oxidative damage and anti-excitotoxic effects of the cannabinoid *in vitro* [303].

Anti-neoplastic activity of THC came into the focus of research after a long-term animal study, designed to investigate THC's potential carcinogenicity, resulted in better survival of rats dosed with THC than controls due to lower incidence for several types of cancer [234]. Frequency of testicular interstitial cell, pancreas and pituitary gland adenomas in male rats, mammary gland fibroadenoma and uterus stromal polyp in female rats was reduced in a dose-related manner. Later studies showed that cannabinoids exerted antineoplastic activity in malignant gliomas [12, 197], malignant skin tumors [304], colorectal cancer [305] and prostate cancer [306]. CB_1 and CB_2 receptor agonists were both effective in some of the studies. Cannabinoids seem to be able to control the cell survival/death decision [307]. Thus, cannabinoids may induce proliferation, growth arrest, or apoptosis in a number of cells depending on dose [307]. Cannabinoids were also shown to inhibit angiogenesis of malignant gliomas by at least two mechanisms, direct inhibition of vascular endothelial cell migration and survival as well as the decrease of the expression of proangiogenic factors [308]. On the other hand it should be noted that the immunosuppressive and proliferative action of THC and other cannabinoids may have unfavorable consequences on cancer growth, especially if tumours do not express cannabinoid receptors [309, 310]. A first human phase I-II trial to investigate the tolerability and efficacy of intracranially applied THC in glioblastoma multiforme is under way in Spain.

Other fields of research with CB agonists include disorders of circulation and blood pressure [162, 311]. In rats, daily application of a CB_1 agonist after experimental infarction prevented signs of heart failure, endothelial dysfunction and hypotension, however, the cannabinoid also increased left-ventricular end-diastolic pressure, which may be negative in the long run [312].

Several effects observed in animal studies provide the basis for further research, among them are effects against diarrhea in mice [313] and stabilization of respiration in sleep-related breathing disorders (e.g. apnea) [314]. Cannabinoids were effective in an animal model of attention-deficit hyperactivity disorder (ADHD), in the spontaneously hypertensive-rat (SHR) [315]. A very impulsive subgroup of SHR rats presented a reduced density of CB_1 cannabinoid receptors in the prefrontal cortex of the brain. The administration of WIN55,212-2 normalized the impulsive behavioral profile in this subgroup, but had no effect on controls.

6.2. Other Cannabinoids

Two other cannabinoids under clinical investigation are HU-211, which is also called dexanabinol, and CT3 or ajulemic acid, which is now called IP751 by Indevus Pharmaceuticals. The cannabis extracts Cannador and Sativex contain considerable amounts of cannabidiol (CBD).

Cannabidiol

The rationale for the combination of THC and CBD is the observation that CBD reduced the psychic side effects of THC, which may result in an improved tolerance of the drug. Simultaneous oral administration of CBD (1 mg/kg) with a high THC dose (0.5 mg/kg) in healthy volunteers attenuated the anxiogenic and psychotomimetic symptoms induced by THC, but not the increase in pulse-rate [200]. Other THC effects including anti-emesis and anti-inflammation may be increased, since these therapeutic properties are shared by CBD, but it cannot be excluded that some therapeutic effects of THC may be antagonized as well.

In small human studies, CBD was shown to exert potent anxiolytic and anti-psychotic effects [210]. Oral CBD (300 mg) attenuated anxiety induced in healthy volunteers by having them prepare a 4-minute speech to a similar extent as ipsapirone (5 mg) and diazepam (10 mg) [316]. In a single case study, CBD in increasing doses up to 1500 mg/day was as effective as an antipsychotic as haloperidol in a schizophrenic patient, who had significant hormonal side effects during treatment with a typical antipsychotic [210].

In an open clinical study with four patients suffering from Huntington's disease, CBD (2 x 300 mg) reduced choreic symptoms in three participants (Sandyk *et al.* 1988, cited from [92]). However, these effects could not be confirmed in a double-blind crossover study with 15 patients [317]. Cannabidiol caused a 20 to 50 per cent reduction in various dystonias of five patients [212]. Results from three controlled clinical studies on CBD in epilepsy were mixed, but the cannabinoid seems to have some anti-epileptic potential [318-320].

Dexanabinol

Dexanabinol or HU-211 is an antagonist of the NMDA subtype (NMDA = N-methyl-D-aspartic acid) of the glutamate receptor [99]. Glutamate is the main excitatory neurotransmitter in the brain, and excessive activation of glutamate receptors may mediate neuronal injury or death in a variety of pathological conditions, including stroke, mechanical brain trauma, hypoxia and various neurodegenerative disorders, including Parkinson's

syndrome, amyotrophic lateral sclerosis, neuropathic pain syndromes and perhaps Alzheimer's disease [321]. HU-211 proved to be neuroprotective in several animal models, including closed head injury in rats [99], a model of focal cerebral ischemia in spontaneously hypertensive rats [322], and optic nerve crush injury in rats [323]. The cannabinoid also reduced the consequences of experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis [324].

So far, HU-211 has been studied in humans for two indications, in severe head trauma and for the prevention of cognitive deficits following coronary artery bypass surgery. In a phase II double blind clinical trial in patients with severe head trauma, dexanabinol attenuated elevations of intracranial pressure and reductions of cerebral perfusion pressure [325]. A consistent trend towards better overall outcome as determined by the Glasgow outcome scale was observed in the severe patient subgroup. However, clinical phase III studies did not confirm efficacy (Press release of Pharmos Corporation of 20 December 2004). A phase II study of dexanabinol for the prevention of cognitive deficits following heart surgery is under way [326].

Ajulemic Acid (CT3, IP751)

The anti-inflammatory activity of CT3 was demonstrated in animal models of acute and chronic inflammation [100]. The animals did not exhibit evidence of tolerance to ajulemic acid during 30 days of treatment; a clear divergence in the mechanism of action between the cannabinoid acids and other cannabinoids. CT3 also markedly reduced the behavioral responses to painful stimuli [100]. In unrelated studies, CT3 appeared to have potent anti-cancer effects [11]. According to a press release by Indevus Pharmaceuticals on 7 March 2005, the drug was effective in an animal model of interstitial cystitis. It significantly reduced the bladder overactivity associated with the disease, without affecting the normal voiding mechanism of the bladder.

In a first clinical study with 20 subjects who suffered from chronic pain, CT3 proved to have a significant analgesic effect without psychic side effects [223].

6.3. Cannabinoid Receptor Antagonists

A possible therapeutic potential of cannabinoid receptor antagonists was proposed for obesity [159], schizophrenia [159], in conditions with lowered blood pressure, e.g. liver cirrhosis [162] and septic shock [327], Parkinson's disease [328], Huntington's disease [329], alcohol and nicotine dependency [330], heroine addiction [331], problems in sexual behavior and sexual performance [110], asthma [110] and to improve memory in Alzheimer's disease [159]. The idea that CB receptor antagonists may be useful in liver cirrhosis follows the observation that rats with carbon tetrachloride-induced liver cirrhosis present with low blood pressure, which is elevated by SR141716A [332]. The antagonist also reduced the elevated mesenteric blood flow and portal pressure. Compared with non-cirrhotic controls, in cirrhotic human livers, there was a three-fold increase in CB_1 receptors on isolated vascular endothelial cells [332]. Recently, it was reported that the density of CB_1 receptors and the levels of anandamide and 2-AG in the dorsolateral prefrontal cortex of alcoholic suicides was higher than in a control group of chronic alcoholics suggesting a hyperactivity of endocannabinoidergic signaling in alcoholic suicides and a therapeutic potential for CB_1 antagonists [333].

Many of the studies on the therapeutic potential of cannabinoid receptor antagonists are found in the basic research literature, and only one paper on clinical research has been published in peer-reviewed journals [334]. The compound most clinically advanced is rimonabant, registered in 2005 for approval in the US and Europe as Acomplia. Phase IIb clinical data showed that rimonabant in daily doses of 5, 10 and 20 mg caused a significant weight loss in a 16-week study (cited according to [335]). Two phase III trials were initiated for the treatment of obesity in August 2001 [336] and by September 2002 for smoking cessation [336]. Results of these trials showed that the drug significantly reduced body weight within one year of treatment (5 or 20 mg rimonabant once daily). The lower dose resulted in a mean weight reduction of 3.4 kg, the higher dose in a mean reduction of 6.6 kg, while the placebo group lost 1.8 kg on average. The higher dose also had a significant positive effect on blood lipids. Results of the smoking cessation study were presented at the 53rd annual scientific meeting of the American College of Cardiology in March 2004. According to a press release by Sanofi-Synthelabo, 700 smokers were treated either with 5 or 20 mg of rimonabant, and about a quarter of the subjects who received 20 mg stopped smoking in 10 weeks, which was about twice the quit rate in the placebo group.

7. SIDE EFFECTS

7.1. Agonists

Adverse effects of medical cannabis use are within the range of effects tolerated for other medications [126, 127]. Long-term medical use of cannabis for more than 15 years has been reported to be well-tolerated without significant physical or cognitive impairment [337].

The median lethal dose (LD_{50}) of oral THC in rats was 800-1900 mg/kg depending on sex and strain [338]. 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) [338]. Acute fatal cases in humans have not been substantiated. However, myocardial infarction may be triggered by THC due to effects on circulation [339, 340]. This is unlikely to happen in healthy subjects but in persons with coronary heart disease for whom orthostatic hypotension or a moderately increased heart rate may pose a risk. The THC derivative nabilone reduced choreatic movements in Huntington`s disease in a single case study [329]. Thus, cannabinoid receptor agonists may be contraindicated in Huntington's disease.

It is controversial whether heavy regular consumption may have a long-term negative impact on cognition [341-343], but this impairment seems to be minimal if it exists [341, 344]. 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 [345].

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 [345]. In a longitudinal study with young adults current heavy cannabis use was associated with reduced overall IQ, processing speed, immediate, and delayed memory, while former heavy users showed no difference to non-users [346]. In a twin study cannabis-using twins significantly differed from their non-using co-twins in general intelligence [347]. However, this difference was minimal and authors concluded that these results indicate an absence of marked long-term residual effects of cannabis use on cognitive abilities. In a meta-analysis of studies that investigated residual effects of cannabis on the neurocognitive performance of adult human subjects, chronic use was associated with decrements in the ability to learn and remember new information, whereas other cognitive abilities were unaffected [348]. There is conflicting evidence that infants exposed to THC *in utero* suffer developmental and cognitive impairment [349].

Cannabis can induce a schizophrenic psychosis in vulnerable persons [124, 135], and there is increasing evidence that there is a distinct cannabis psychosis [350] and that cannabis increases the risk to develop a psychosis by two-fold [351].

Cannabis use is associated with depression, suicidal thoughts and attempted suicide [352]. However, a study with dizygotic and monozygotic twins suggests that this association may not be causal and that genetic vulnerabilities make substantial contributions, since the association was higher in dizygotic than in identical twins [352]. Heavy cannabis use has been reported to cause an "amotivational syndrome" [353]. A systematical examination of the mental health of cannabis users suggests that symptoms associated with this syndrome are due to depression [353].

The consequences of the use of THC or cannabis by patients with liver cirrhosis are unclear. In experimental studies, activation of the CB_2 receptor was shown to cause antifibrogenic effects [354]. In liver biopsy specimens from patients with active cirrhosis of various etiologies, CB_2 receptors were expressed in non-parenchymal cells. In contrast, CB_2 receptors were not detected in normal human liver. In cultured hepatic myofibroblasts and in activated hepatic stellate cells activation of CB_2 receptors triggered potent antifibrogenic effects, namely, growth inhibition and apoptosis. On the other, hand an epidemiological study presented by Hezode *et al.* at the 39th Annual European Association for the Study of the Liver Conference in April 2004 suggests that daily use of cannabis may promote the development of liver cirrhosis in persons with chronic hepatitis C, while moderate use did not increase the risk. The endocannabinoid system was proposed to play an important role in the vasodilated state in advanced cirrhosis, and anandamide is regarded as a selective splanchnic vasodilator [198]. Thus, the use of cannabinoids may have unfavorable effects in advanced liver cirrhosis.

The harmful effects of combustion products produced by smoking cannabis have to be distinguished from effects by cannabis or single cannabinoids [127]. The risks of smoking cannabis are probably similar to those from smoking other dried plant material, including tobacco [355].

Tolerance develops to most of the THC effects [356], among them being the cardiovascular, psychological and skin hypothermic effects [357, 358], analgesia [359], immunosuppression [360], corticosteroid release [361], and disruption of the hypothalamo-hypophyseal axis [362], causing alterations in endocannabinoid formation and contents in the brain [363]. In a 30-day study, volunteers received daily doses of 210 mg oral THC and developed tolerance to cognitive and psychomotor impairment and to the psychological high by the end of the study [357]. After a few days, an increased heart rate was replaced by a normal or a slowed heart rate. Tolerance develops also to cannabinoid-induced orthostatic hypotension [154].

Tolerance can mainly be attributed to pharmacodynamic changes, presumably based on receptor downregulation and/or receptor desensitization [363, 364]. Rate and duration of tolerance varies with different effects. Rats receiving THC over a period of five days exhibited a decreased specific binding ranging from 20 to 60% in different receptor sites of the brain compared to controls [356]. However, in another study, no significant alteration in receptor binding was observed after chronic administration of THC resulting in twenty-sevenfold behavioral tolerance [365]. Chronic administration of anandamide as well, resulted in behavioral tolerance without receptor downregulation [366], and it was proposed that desensitization of the CB_1 receptor might account for this observation [366]. Tolerance has been observed to occur together with modified biotransformation activities with regard to mitochondrial oxygen consumption, monooxygenase activities, and the content of liver microsomal cytochrome P450 [367]. However, only a small proportion of tolerance can be attributed to changes in metabolism [368].

After abrupt cessation of chronic dosing with THC, especially with high doses, withdrawal has been observed in humans [357, 369]. 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 [370-372]. A review of several indicators of the abuse potential of oral dronabinol in a therapeutic context found little evidence of such a problem [373].

7.2. Antagonists

A 90-mg dose of rimonabant was well-tolerated in healthy subjects with a history of cannabis use [159]. In current clinical studies, doses of 5 to 20 mg are used. Adverse effects with rimonabant are reported to be transient and slightly greater than placebo, with the most common being nausea [334, 374]. A high drop-out rate was reported for rimonabant's phase III studies in the press (New York Times of 5 December 2004) which may be due to taste aversion [375] and anxiety-like responses [376].

Further possible side effects of CB_1 receptor antagonists might be appetite loss [377] and other inverse agonistic actions at the CB_1 receptor observed *in vivo*, including hyperalgesia [78] and inflammation. There is a report of a subject who developed multiple sclerosis after starting treatment with rimonabant for obesity [378], an effect consistent with reported protective effects of endocannabinoids in animal models of multiple sclerosis [73].

8. DRUG INTERACTIONS

The knowledge of drug interactions is restricted to THC, nabilone and cannabis, which are in use for a considerable time. Not much knowledge is available for other cannabinoids and cannabinoid receptor antagonists. Interactions of THC and cannabis with other drugs may depend on activity on similar effector systems or metabolic interactions [380]. Since cannabinoids are strongly bound to proteins, interactions with other protein bound drugs may also occur. They might also interact with drugs that, such as THC, are metabolized by enzymes of the cytochrome P-450 complex. However, there was only a minor influence of cannabis smoking and oral dronabinol on pharmacokinetic parameters of antiretroviral medication used in HIV infection and metabolized by cytochrome P-450 enzymes, and the use of cannabinoids was regarded as unlikely to impair antiretroviral efficacy [380]. Tobacco and cannabis smoking cessation was reported to result in elevated blood levels of antipsychotic medication (clozapine or olanzapine), due to cessation of induction of cytochrome $P450_{1A2}$ (CYP_{1A2}) by smoke constituents [381].

Other medicines may enhance or attenuate certain actions of THC or certain actions of these medicines may be enhanced or attenuated by THC [382, 383]. 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 [384]. Cannabis, caffeine and tobacco reduced the blood pressure reactivity protection of ascorbic acid, probably through their dopaminergic effects [385].

Of greatest clinical relevance is reinforcement of the sedating effects of other psychotropic substances (alcohol, benzodiazepines), and the interaction with substances that act on heart and circulation (amphetamines, adrenaline, atropine, beta-blockers, diuretics, tricyclic antidepressants, etc.) [382, 383].

A number of additive effects may be desirable, such as the enhancement of muscle relaxants, bronchodilators and anti-glaucoma medication [180] of analgesia by opiates [265, 267], the antiemetic effect of phenothiazines [384] and 5-HT_3 antagonists [246], and the antiepileptic action of benzodiazepines [386]. THC may antagonize the antipsychotic actions of neuroleptics [383] and may improve their clinical responsiveness in motor disorders [387]. A combination with other drugs may be desirable not only to reduce side effects of the single drugs, but also to prevent the development of tolerance. In animals studies, tolerance to morphine was reduced by simultaneous administration of THC [388]. Chronic treatment with high doses of oral morphine produced a threefold tolerance of pain-reducing effects. Tolerance to morphine was prevented in groups receiving a daily co-treatment with low doses of THC [388].

Since the cannabinoid system is linked with hormonal control, there may be interactions in this area. The progesterone receptor inhibitor mifepristone, which is approved for the termination of early pregnancy, and the glucocorticoid synthesis inhibitor, metyrapone, were shown to potentiate the sedating effects of high THC doses in mice [389].

The cyclooxygenase inhibitors indomethacin, acetylsalicylic acid, and other non-steroidal anti-inflammatory drugs antagonize THC effects. Indomethacin significantly reduced subjective "high" [390], tachycardia [390], decrease of contractile performance in heart muscle [391] and decrease of intraocular pressure following topical THC (eye drops) [392], reflecting the involvement of cyclooxygenase activity in several THC effects.

9. CONCLUSION

The cannabinoid system plays a major role in signal transduction in neuronal cells, and anandamide seems to be a central inhibitory compound in the central nervous system [393]. Modulators of the cannabinoid system with therapeutic potential include agonists and antagonists at both receptors subtypes and inhibitors of endocannabinoid degradation. Mechanisms of action of endogenous and exogenous cannabinoids are complex, not only involving activation of and interaction at the cannabinoid receptor, but also activation of vanilloid receptors [197], influence of endocannabinoid concentration [202], antioxidant activity [116], metabolic interaction with other compounds, and several others.

Due to the millennia-long use of cannabis for recreational, religious and medicinal purposes, which in recent decades was accompanied by scientists from several disciplines, medical CB receptor agonism is predicted to exhibit previously described side effects or adverse events. On the other hand, information on possible side effects of antagonists is still sparse, albeit they usually seem to be well-tolerated in clinical studies.

The psychotropic effects of CB_1 receptor agonists and the stigma of cannabis as a recreational and addicting drug are still major obstacles to the legal therapeutic utilization of the whole range of potentially beneficial effects. In recent years, large and properly designed clinical studies have been conducted and further trials are under way or planned to verify anecdotic experiences and the results from smaller uncontrolled studies, and to overcome uncertainties and skepticism.

Apart from CB_1 receptor agonists and cannabis preparations that cause psychic side effects, cannabinoid

analogs that do not bind to the CB_1 receptor are attractive compounds for clinical research. 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 or hydrolysis. Inhibitors of endocannabinoid degradation may exert the maximum effect in brain areas where endocannabinoid levels are already increased in reaction to a disease. It is remarkable that FAAH inhibitors may already be in clinical use [394]. The non-steroidal anti-inflammatory agent flurbiprofen, inhibits the metabolism of FAAH and intrathecally administrated flurbiprofen reduced inflammatory pain by a mechanism that was blocked by a CB_1 receptor antagonist. The anaesthetic agent propofol and the non-steroidal anti-inflammatory drugs indomethacin also activate cannabinoid receptors as an important part of their actions [394].

The discovery of the cannabinoid system has accelerated a broad and exciting field of research, and we are in the middle of discovering all its facets that may be of use for the prevention and treatment of illnesses.

ABBREVIATIONS

Δ^9-THC	=	Δ^9-Tetrahydrocannabinol (dronabinol)
2-AG	=	2-Arachidonoyl glycerol
5-HT	=	5-Hydroxytryptamine
ACEA	=	Arachidonoyl-2'-chloroethylamide
ACPA	=	Arachidonoyl cyclopropylamide
AD	=	Alzheimer's disease
ADHD	=	Attention-deficit hyperactivity disorder
ADL	=	Activities of daily living
AEA	=	Arachidonoyl ethanolamide (anandamide)
ART	=	Antiretroviral therapy
cAMP	=	Cyclic adenosine monophosphate
CB receptor	=	Cannabinoid receptor
CBC	=	Cannabichromene
CBD	=	Cannabidiol
CBG	=	Cannabigerol
CBN	=	Cannabinol
CNR	=	Cannabinoid receptor gene
COX	=	Cyclooxygenase
CREAE	=	Chronic relapsing experimental autoimmune encephalomyelitis
$CRHR_1$	=	Corticotropin releasing hormone receptor 1
DMHP	=	Dimethylheptyl-tetrahydrocannabinol
DNA	=	Deoxyribonucleic acid
EAE	=	Experimental autoimmune encephalo-myelitis
ERK	=	Extracellular signal-regulated kinase
FAAH	=	Fatty acid amide hydrolase
GABA	=	γ-aminobutyric acid
GPCR	=	G-protein-coupled receptors
NADA	=	*N*-arachidonoyl-dopamine
NMDA	=	N-methyl-D-aspartic acid
NO	=	Nitric oxide
NOS	=	Nitric oxide synthase
NSAID	=	Non-steroidal anti-inflammatory drug
PMSF	=	Phenylmethylsulfonyl fluoride
PPARgamma	=	Peroxisome proliferator-activated receptor gamma
SHR	=	Spontaneously hypertensive-rat
Th	=	T helper
TNF	=	Tumor necrosis factor
VR	=	Vanilloid receptor

REFERENCES

[1] Fankhauser, M. In *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential.* Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *4*, pp. 37-51.

[2] Russo; E. In *The Medicinal Uses of Cannabis and Cannabinoids*. Guy, G.W.; Whittle, B.; Robson, P.; Eds.; Pharmaceutical Press: London, Chicago, **2004;** Vol. *1*, pp. 2-16.

[3] Loewe, S. *Archiv für Experimentelle Pathologie und Pharmakologie*, **1950**, *211*, 175.

[4] Davis, J.P.; Ramsey, H.H. *Fed. Proc.*, **1949**, *8*, 284.

[5] Stockings, G.T. *BMJ*, **1947**, *1*, 918.

[6] Thompson, L.J.; Proctor, R.C. *N Carolina. Med. J.*, **1953**, *14*, 520.

[7] Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.*, **1964**, *86*, 1646.

[8] Matsuda, L.A.; Lolait, S.J.; Brownstein, M.; Young, A.; Bonner, T.I. *Nature*, **1990**, *346*, 561.

[9] Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature*, **1993**, *365*, 61.

[10] Howlett, A.C. *Prostaglandins Other Lipid Mediat.,* **2002**, *68*(69), 619.

[11] Recht, L.D.; Salmonsen, R.; Rosetti, R.; Jang, T.; Pipia, G.; Kubiatowski, T.; Karim, P.; Ross, A.H; Zurier, R.; Litofsky, NS.; Burstein, S. *Biochem. Pharmacol.*, **2001,** *62(6)*, 755.

[12] Sanchez, C.; de Ceballos, M.L.; del Pulgar, T.G.; Rueda, D.; Corbacho, C.; Velasco, G.; Galve-Roperh, I.; Huffman, J.W.; Ramon y Cajal, S.; Guzman, M. *Cancer Res.*, **2001**, *61(15)*, 5784.

[13] De Petrocellis, L.; Melck, D.; Bisogno, T.; Milone, A.; Di Marzo, V. *Neuroscience*, **1999**, *92(1)*, 377.

[14] McPartland, J.M.; Pruitt, P.I. *J. Cannabis. Ther.*, **2002**, *2*, 73.

[15] Chakrabarti, A.; Onaivi, E.S.; Chaudhuri, G**.** *DNA Seq.*, **1995**, *5(6);* 385.

[16] Shire, D.; Calandra, B.; Rinaldi-Carmona, M.; Oustric, D.; Pessegue, B.; Bonnin-Cabanne, O.; Le Fur, G.; Caput, D.; Ferrara, P. *Biochim. Biophys. Acta.*, **1996**, *1307(2)*, 132.

[17] Mukherjee, S.; Adams, M.; Whiteaker, K.; Daza, A.; Kage, K.; Cassar, S.; Meyer, M.; Yao, B.B. *Eur. J. Pharmacol.*, **2004**, *505*, 1.

[18] Rinaldi-Carmona, M.; Calandra, B.; Shire, D.; Bouaboula, M.; Oustric, D.; Barth, F.; Casellas, P.; Ferrara, P.; Le Fur, G. *J. Pharmacol. Exp. Ther.*, **1996**, *278(2)*, 871.

[19] Ryberg, E.; Vu, H.K.; Larsson, N.; Groblewski, T.; Hjorth, S.; Elebring, T.; Sjogren, S.; Greasley, P.J. *FEBS Lett.*, **2005**, *579(1)*, 259.

[20] Ujike, H.; Morita, Y. *J. Pharmacol. Sci.*, **2004**, *96(4)*, 376.

[21] Barrero, F.J.; Ampuero, I.; Morales, B.; Vives, F.; de Dios Luna Del Castillo, J.; Hoenicka, J.; Garcia Yebenes, J. *Pharmacogenomics. J.*, **2005**, *5(2)*, 135.

[22] Preuss, U.W.; Koller, G.; Zill, P.; Bondy, B.; Soyka, M. *Eur. Arch. Psychiatry Clin. Neurosci.*, **2003**, *253(6)*, 275.

[23] Gadzicki, D.; Muller-Vahl, K.R.; Heller, D.; Ossege, S.; Nothen, M.M.; Hebebrand, J.; Stuhrmann, M. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.*, **2004**, *127(1)*, 97.

[24] Bockaert, J.; Pin, J.P. *EMBO. J.*, **1999**, *18*, 1723.
[25] Pertwee, R.G. *Pharmacol. Ther.*, **1997**, *74(2)*, 129.
[26] Pertwee, R. In *The Medicinal Uses of Cannabis and Cannabinoids*. Guy, G.W.; Whittle, B.; Robson, P.; Eds.; Pharmaceutical Press: London, Chicago, **2004**; Vol. *5*, pp. 103-139.
[27] Pertwee, R.G. In *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential.* Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *7*, pp. 73-88.
[28] Galiègue, S.; Mary, S.; Marchand, J.; Dussossoy, D.; Carrière, D.; Carayon, P.; Bouaboula, M.; Shire, D.; Le Fur, G.; Casellas, P. *Eur. J. Biochem.*, **1995**, *232*, 54.
[29] Ibrahim, M.M.; Porreca, F.; Lai, J.; Albrecht, P.J.; Rice, F.L.; Khodorova, A.; Davar, G.; Makriyannis, A.; Vanderah, T.W.; Mata, H.P.; Malan, T.P. Jr. *Proc. Natl. Acad. Sci. USA*, **2005**, *102(8)*, 3093.
[30] Pfitzer, T.; Niederhoffer, N.; Szabo, B. *Naunyn Schmiedebergs Arch. Pharmacol.*, **2005**, *371(1)*, 9.
[31] Varvel, S.A.; Anum, E.; Niyuhire, F.; Wise, L.E.; Lichtman, A.H. *Psychopharmacology (Berl)*, **2005**, *178(2-3)*, 317.
[32] Braida, D.; Pozzi, M.; Cavallini, R.; Sala, M. *Neuroscience*, **2001**, *104*, 923.
[33] Tanda, G.; Pontieri, F.E.; Di Chiara, G. *Science*, **1997**, *276(5321)*, 2048.
[34] Domino, E.F. In *Marihuana and medicine*. Nahas, G.; Sutin, K.M.; Harvey, D.J.; Agurell. S.; Eds.; Humana Press: Totowa NJ, **1999**; Vol. *14*, pp. 223-226.
[35] Mattes, R.D.; Shaw, L.M.; Engelman. K. *Chem Senses.*, **1994**, *19(2)*, 125.
[36] Fan, P. *J. Neurophysiol.*, **1995**, *73(2)*, 907.
[37] Musty, R.E.; Consroe, P. In *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential*, Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *17*, pp. 195-204.
[38] Hagenbach, U.; Luz, S.; Ghafoor, N.; Berger, J.M.; Grotenhermen, F.; Brenneisen, R.; Mäder, M. *Spinal Cord*, **2005**, *submitted* for publication.
[39] Fabre, L.F.; McLendon, D. *J. Clin. Pharmacol.*, 1981, *21(8-9 Suppl)*, 377.
[40] Kearn, C.S.; Blake-Palmer, K.; Daniel, E.; Mackie, K.; Glass, M. *Mol. Pharmacol.*, **2005**, *67(5)*, 1697.
[41] Hermann, H.; Lutz, B. *Neurosci. Lett.*, **2005**, *375(1)*, 13.
[42] Salio, C.; Fischer, J.; Franzoni, M.F.; Mackie, K.; Kaneko, T.; Conrath, M. *Neuroreport.*, **2001**, *12(17)*, 3689.
[43] Lichtman, A.H.; Sheikh, S.M.; Loh, H.H.; Martin, B.R. *J. Pharmacol. Exp. Ther.*, **2001**, *298(3)*, 1007.
[44] Wachtel, S.R.; de Wit, H. *Drug Alcohol Depend.*, **2000**, *59(3)*, 251.
[45] Haney, M.; Bisaga, A.; Foltin, R.W. *Psychopharmacology (Berl)*, **2003**, *166(1)*, 77.
[46] Gertsch, J.; Schoop, R.; Kuenzle, U.; Suter, A. *FEBS Lett.*, **2004**, *577(3),* 563.
[47] Kaplan, B.L.; Ouyang, Y.; Rockwell, C.E.; Rao, G.K.; Kaminski, N.E. *J. Leukoc. Biol.*, **2005**, *77(6)*, 966.
[48] Vaccani, A.; Massi, P.; Colombo, A.; Rubino, T.; Parolaro, D. *Br. J. Pharmacol.*, **2005**, *144(8)*, 1032.
[49] Di Marzo, V.; Breivogel, C.S.; Tao, Q.; Bridgen, D.T.; Razdan, R.K.; Zimmer, A.M.; Zimmer, A.; Martin. B.R. *J. Neurochem.*, **2000**, *75(6)*, 2434.
[50] Fride, E.; Foox, A.; Rosenberg, E.; Faigenboim, M.; Cohen, V.; Barda, L.; Blau, H.; Mechoulam. R. *Eur. J. Pharmacol.*, **2003**, *461(1)*, 27.
[51] Wiley, J.L.; Martin, B.R. *Chem. Phys. Lipids*, **2002**, *121(1-2)*, 57.
[52] Devane, W.A.; Hanus, L.; Breuer, A.; Pertwee, R.G.; Stevenson, L.A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam. R. *Science*, **1992**, *258(5090)*, 1946.
[53] Giuffrida, A.; Beltramo, M.; Piomelli, D. *J. Pharmacol. Exp. Ther.*, **2001**, *298(1)*, 7.
[54] Sugiura, T.; Kondo, S.; Sukagawa, A.; Nakane, S.; Shinoda, A.; Itoh, K.; Yamashita, A.; Waku, K. *Biochem. Biophys. Res. Commun.*, **1995**, *215(1)*, 89.
[55] Mechoulam, R.; Ben-Shabat, S.; Hanus, L.; Ligumsky, M.; Kaminski, N.E.; Schatz, A.R.; Gopher, A.; Almog, S.; Martin, B.R.; Compton, D.R. *Biochem. Pharmacol.*, **1995**, *50(1)*, 83.
[56] Hanus, L.; Abu-Lafi, S.; Fride, E.; Breuer, A.; Vogel, Z.; Shalev, D.E.; Kustanovich, I.; Mechoulam, R. *Proc Natl. Acad. Sci. USA*, **2001**, *98(7)*, 3662.
[57] Porter, A.C.; Sauer, J.M.; Knierman, M.D.; Becker, G.W.; Berna, M.-J.; Bao, J.; Nomikos, G.G.; Carter, P.; Bymaster, F.P.; Leese, A.B.; Felder, C.C. *J. Pharmacol. Exp. Ther.*, **2002**, *301(3)*, 1020.
[58] Huang, S.M.; Bisogno, T.; Trevisani, M.; Al-Hayani, A.; De Petrocellis, L.; Fezza, F.; Tognetto, M.; Petros, T.J.; Krey, J.F.; Chu, C.J.; Miller, J.D.; Davies, S.N.; Geppetti, P.; Walker, J.M.; Di Marzo. V. *Proc. Natl. Acad. Sci. USA*, **2002**, *99(12)*, 8400.
[59] Oka, S.; Tsuchie, A.; Tokumura, A.; Muramatsu, M.; Suhara, Y.; Takayama, H.; Waku, K.; Sugiura, T. *J. Neurochem.*, **2003** Jun, 85*(6)*, 1374.
[60] Steffens, M.; Zentner, J.; Honegger, J.; Feuerstein, T.J. *Biochem. Pharmacol.*, **2005**, *69(1)*, 169.
[61] Gonsiorek, W.; Lunn, C.; Fan, X.; Narula, S.; Lundell, D.; Hipkin, R.W. *Mol. Pharmacol.*, **2000**, *57(5)*, 1045.
[62] Sagar, D.R.; Smith, PA.; Millns, P.J.; Smart, D.; Kendall, D.A.; Chapman, V. *Eur. J. Neurosci.*, **2004**, 20*(1)*, 175.
[63] Al-Hayani, A.; Wease, K.N.; Ross, R.A.; Pertwee, R.G.; Davies, S.N. *Neuropharmacology*, **2001**, *41(8)*, 1000.
[64] Stander, S.; Moormann, C.; Schumacher, M.; Metze, D.; Luger, T.A.; Steinhoff, M. *Exp. Dermatol.*, **2005**, *14(2)*, 155.
[65] Craib, S.J; Ellington, H.C.; Pertwee, R.G.; Ross, R.A. *Br. J. Pharmacol.*, **2001**, *134(1)*, 30.
[66] O'Sullivan, S.E.; Kendall, D.A.; Randall, M.D. *Br. J. Pharmacol.*, **2004**, *141(5)*, 803.
[67] Di Marzo, V.; Fontana, A.; Cadas, H.; Schinelli, S.; Cimino, G.; Schwartz, J.C.; Piomelli, D. *Nature*, **1994**, *372(6507)*, 686.
[68] Di Marzo, V. Biochim. Biophys. Acta., **1998**, 1392(2-3), 153.
[69] Cravatt, B.F.; Demarest, K.; Patricelli, M.P.; Bracey, M.H.; Giang, D.K.; Martin, B.R.; Lichtman, A.H. *Proc. Natl. Acad. Sci.*, *USA* **2001**, *98*, 9371.
[70] Fezza, F.; Bisogno, T.; Minassi, A.; Appendino, G.; Mechoulam, R.; Di Marzo, V. *FEBS Lett.*, **2002**, *513(2-3)*, 294.
[71] Fowler, C.J.; Jacobsson, S.O. *Prostaglandins Leukot. Essent Fatty Acids*, **2002**, *66*(2-3), 193.
[72] Di Marzo, V.; Griffin, G.; De Petrocellis, L.; Brandi, I.; Bisogno, T.; Williams, W.; Grier, M.C.; Kulasegram, S.; Mahadevan, A.; Razdan, R.K.; Martin. B.R. *J. Pharmacol. Exp. Ther.*, **2002**, *300(3)*, 984.
[73] Baker, D.; Pryce, G.; Croxford, J.L.; Brown, P.; Pertwee, R.G.; Makriyannis, A.; Khanolkar, A.; Layward, L.; Fezza, F.; Bisogno, T.; Di Marzo, V. *FASEB J.*, **2001**, *15*, 300.
[74] Glaser, S.T.; Abumrad, N.A.; Fatade, F.; Kaczocha, M.; Studholme, K.M.; Deutsch, D.G. *Proc. Natl. Acad. Sci. USA*, **2003**, *100(7)*, 4269.
[75] Chiang, K.P.; Gerber, A.L.; Sipe, J.C.; Cravatt, B.F. *Hum. Mol. Genet.*, **2004**, *13(18)*, 2113.
[76] Morita, Y; Ujike, H.; Tanaka, Y.; Uchida, N.; Nomura, A.; Ohtani, K.; Kishimoto, M.; Morio, A.; Imamura, T.; Sakai, A.; Inada, T.; Harano, M.; Komiyama, T.; Yamada, M.; Sekine, Y.; Iwata, N.; Iyo, M.; Sora, I.; Ozaki, N.; Kuroda, S. *Neurosci. Lett.*, **2005**, *376(3)*, 182.
[77] Sipe, J.C.: Waalen, J.; Gerber, A.; Beutler, E. *Int. J. Obes. Relat. Metab. Disord.*, **2005**, *29(7)*, 755.
[78] Jaggar, S.I.; Hasnie, F.S.; Sellaturay, S.; Rice. A.S. *Pain*, **1998**, *76(1-2)*, 189.
[79] Chapman, V. *Br. J. Pharmacol.*, **1999**, *127*, 1765.
[80] Walker, J.M.; Huang, S.M.; Strangman, N.M.; Tsou, K.; Sanudo-Pena, M.C. *Proc. Natl. Acad. Sci. USA*, **1999**, *96(21)*, 12198.
[81] Siegling, A.; Hofmann, H.A.; Denzer, D.; Mauler, F.; De Vry, J. *Eur. J. Pharmacol.*, **2001**, *415(1)*, R5.
[82] Izzo, A.A.; Fezza, F.; Capasso, R.; Bisogno, T.; Pinto, L.; Iuvone, T.; Esposito, G.; Mascolo, N.; Di Marzo, V.; Capasso. F. *Br. J. Pharmacol.*, **2001**, *134(3)*, 563.
[83] Di Marzo, V.; Goparaju, S.K.; Wang, L.; Liu, J.; Batkai, S.; Jarai, Z.; Fezza, F.; Miura, G.I.; Palmiter, R.D.; Sugiura, T.; Kunos, G. *Nature*, **2001**, *410(6830)*, 822.
[84] Darmani, N.A. *Pharmacol. Biochem. Behav.*, **2001**, *69*, 239.
[85] Leweke, F.M.; Giuffrida, A.; Wurster, U.; Emrich, H.M.; Piomelli, D. *Neuroreport*, **1999**, *10(8)*, 1665

[86] Beaulieu, P.; Bisogno, T.; Punwar, S.; Farquhar-Smith, W.P.; Ambrosino, G.; Di Marzo, V.; Rice, A.S. *Eur. J. Pharmacol.*, **2000**, *396*, 85.

[87] Razdan, R.K. *Pharmacol. Rev.*, **1986**, *38*, 75.

[88] Pate, D. In *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential.* Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *19*, pp. 215-24.

[89] Di Marzo, V.; Fontana, A. *Essent. Fatty. Acids.*, **1995**, *53*, 1.

[90] Toyota, M.; Shimamura, T.; Ishii, H.; Renner, M.; Braggins, J.; Asakawa, Y. *Chem. Pharm. Bull. (Tokyo)*, **2002**, *50(10)*, 1390.

[91] ElSohly, M.A. In *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential*, Grotenhermen, F.; Russo. E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *3*, pp. 27-36.

[92] Musty, R.E. In *The Medicinal Uses of Cannabis and Cannabinoids*. Guy; G.W.; Whittle; B.; Robson; P.; Eds.; Pharmaceutical Press: London; Chicago, **2004**; Vol. *7*, pp. 165-204.

[93] Lemberger, L.; Crabtree, R.E.; Rowe. H.M. *Science*, **1972**, *177(43)*, 62.

[94] Perez-Reyes, M.; Timmons, M.; Lipton, M.; Davis, K.; Wall. M. *Science*, **1972**, *177(49)*, 633.

[95] Archer, R.A.; Stark, P.; Lemberger, L. *Cannabinoids as therapeutic agents* **1986**, *85*, 103.

[96] Little, P.J.; Compton, D.R.; Mechoulam, R.; Martin, B. *Pharmacol. Biochem. Behav.*, **1989**, *32*, 661.

[97] Ottani, A.; Giuliani, D. *CNS Drug Rev.*, **2001**, *7(2)*, 131.

[98] Titishov, N.; Mechoulam, R.; Zimmerman, A.M. *Pharmacology.*, **1989**, *39(6)*, 337.

[99] Mechoulam, R.; Shohami, E.; In *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential*. Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *36*, pp. 389-398.

[100] Burstein, S. In *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential*. Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *35,* pp. 381-388.

[101] Jain, A.K.; Ryan, J.R.; McMahon, F.G.; Smith, G. *J. Clin. Pharmacol.*, **1981**, *21*, 320.

[102] Citron, M.L.; Herman, T.S.; Vreeland, F.; Krasnow, S.H.; Fossieck, Jr., B.E. *Cancer Treat. Rep.*, **1985**, *69*, 109.

[103] Lucraft, H.H.; Palmer. M.K. *Clin. Radiol.*, **1982**, *33(6)*, 621.

[104] Showalter, V.M.; Compton, D.R.; Martin, B.R.; Abood, M.E. *J. Pharmacol. Exp. Ther.*, **1996**, *278(3)*, 989.

[105] Melvin, L.S.; Milne, G.M.; Johnson, M.R.; Subramaniam, B.; Wilken, G.H.; Howlett, A.C. *Mol. Pharmacol.*, **1993**, *44(5)*, 1008.

[106] Giuffrida, A.; Rodriguez de Fonseca, F.; Nava, F.; Loubet-Lescoulie, P.; Piomelli, D. *Eur J. Pharmacol.*, **2000**, *408(2)*, 161.

[107] Deutsch, D.G.; Lin, S; Hill, W.A.; Morse, K.L.; Salehani, D.; Arreaza, G.; Omeir, RL.; Makriyannis, A. *Biochem. Biophys. Res. Commun.*, **1997**, *231(1)*, 217.

[108] Boger, D.L.; Sato, H.; Lerner, A.E.; Hedrick, M.P.; Fecik, R.A.; Miyauchi, H.; Wilkie, G.D.; Austin, B.J.; Patricelli, M.P.; Cravatt, B.F. *Proc. Natl. Acad. Sci. USA*, **2000**, *97(10)*, 5044.

[109] Rinaldi-Carmona, M.; Barth, F.; Millan, J.; Derocq, J-M.; Casellas, P.; Congy, C.; Oustric, D.; Sarran, M.; Bouaboula, M.; Calandra, B.; Portier, M.; Shire, D.; Breliere, J-C.; Le Fur, G. *J. Pharmacol. Exp. Ther.*, **1998**, *284*, 644.

[110] Lange, J.H.; Kruse, CG. *Curr. Opin. Drug Discov. Devel.*, **2004**, 7*(4)*, 498.

[111] Pertwee, R.G. *Curr. Med. Chem.*, **1999**, *6*, 635.

[112] Plasse, T. In *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential*. Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *14*, pp. 165-180.

[113] Dewey, W.L. *Pharmacol. Rev.*, **1986**, *38(2)*, 151.

[114] Hanus, L.O.; Tchilibon, S.; Ponde, D.E.; Breuer, A.; Fride, E.; Mechoulam, R. *Org. Biomol. Chem.*, **2005**, *3(6)*, 1116.

[115] Bueb, J.L.; Lambert, D.M.; Tschirhart. E.J. *Biochim. Biophys. Acta.*, **2001**, *1538*, 252.

[116] Hampson, A. In *Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential*, Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *9*, pp. 101-10.

[117] Parker, L.A.; Mechoulam, R.; Schlievert, C.; Abbott, L.; Fudge, M.L.; Burton, P. *Psychopharmacology (Berl)*, **2003**, *166(2)*, 156.

[118] Abrahamov, A.; Mechoulam, R. *Life. Sci.*, **1995**, *56*, 2097.

[119] Barann, M.; Molderings, G.; Bruss, M.; Bonisch, H.; Urban, B.W.; Gothert, M. *Br. J. Pharmacol.*, **2002**, *137*, 589.

[120] Adams, I.B.; Martin, B.R. *Addiction*, **1996**, *91*, 1585.

[121] Grotenhermen, F. *Neuroendocrinol. Lett.*, **2004**, *25*, 14.

[122] Guy, G.W.; Whittle, B.; Robson, P. *The medicinal uses of cannabis and cannabinoids*. Pharmaceutical Press: London, Chicago, **2004**.

[123] Grotenhermen, F.; Russo, E. Cannabis and cannabinoids. Pharmacology, toxicology, and therapeutic potential. Haworth Press: Binghamton NY, **2002**.

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

[125] Hollister, L.E. *Pharmacological Reviews*, **1986**, *38*, 1.

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

[127] Joy, J.E.; Watson, S.J.; Benson, J.A. *Marijuana and medicine, Assessing the science base*. Institute of Medicine, National Academy Press: Washington DC, **1999**.

[128] Kalant, H.; Corrigal, W.; Hall, W.; Smart, R. *The health effects of cannabis*. Centre for Addiction and Mental Health, Toronto, **1999**.

[129] Sulcova, E.; Mechoulam, R.; Fride, E. *Pharmacol. Biochem. Behav.*, **1998**, *59(2)*, 347.

[130] Freemon, F.R. *JAMA*, **1972**, *220(10)*, 1364.

[131] Lissoni, P.; Resentini, M.; Mauri, R.; Esposti, D.; Esposti, G.; Rossi, D.; Legname, G.; Fraschini, F. *Horm. Metab. Res.*, **1986**, *18(1)*, 77.

[132] Hampson, R.E.; Deadwyler, S.A. *Life Sci.*, **1999**, *65*, 715.

[133] Heyser, C.J.; Hampson, R.E.; Deadwyler, S.A. *J. Pharmacol. Exp. Ther.*, **1993**, *264(1)*, 294.

[134] Slikker, W. Jr.; Paule, M.G.; Ali, S.F.; Scallet, A.C.; Bailey, J.R. In *Marijuana/Cannabinoids, neurobiology and neurophysiology.* Murphy, L.; Bartke, A.; Eds.; CRC Press: Boca Raton FL, **1992**; Vol. 7, pp. 219-273.

[135] Solowij, N.; Grenyer, B.F.S. In *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential*. Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *27*, pp. 299-312.

[136] Kelly, T.H.; Foltin, R.W.; Emurian, C.S.; Fischman, M.W. *J. Anal. Toxicol.*, **1993**, *17(5)*, 264.

[137] Kelleher, L.M.; Stough, C.; Sergejew. A.A.; Rolfe, T. *Addict. Behav.*, **2004**, *29(6)*, 1213.

[138] Perez-Reyes, M. In *Marihuana and medicine*. Nahas, G.; Sutin, K.M.; Harvey, D.J.; Agurell. S.; Eds.; Humana Press: Totowa NJ, **1999**; Vol. *17*, pp. 245-52.

[139] Müller-Vahl, K.R.; Prevedel, H.; Theloe, K.; Kolbe, H.; Emrich, H.M.; Schneider, U. *Neuropsychopharmacology*, **2003**, *28(2)*, 384.

[140] Patel, S.; Roelke, C.T.; Rademacher, D.J.; Cullinan, W.E.; Hillard, C.J. *Endocrinology*, **2004** 145*(12)*, 5429.

[141] Hill, M.N.; Patel, S.; Carrier, E.J.; Rademacher, D.J.; Ormerod, B.K.; Hillard, C.J.; Gorzalka, B.B. *Neuropsychopharmacology*, **2005**, *30(3)*, 508.

[142] Patel, S.; Cravatt, BF.; Hillard, C.J. *Neuropsychopharmacology*, **2005**, *30(3)*, 497.

[143] Marsicano, G.; Wotjak, C.T.; Azad, S.C.; Bisogno, T.; Rammes, G.; Cascio, M.G.; Hermann, H.; Tang, J.; Hofmann, C.; Zieglgänsberger, W.; Di Marzo, V.; Lutz, B. *Nature*, **2002**, *418 (6897),* 530.

[144] Chhatwal, J.P.; Davis, M.; Maguschak, K.A.; Ressler, K.J. *Neuropsychopharmacology*, **2005**, *30(3)*, 516.

[145] Mechoulam, R. Prostaglandins Leukot. Essent Fatty Acids, **2002**, 66(2-3), 93.

[146] Grundy, R.I. Expert. Opin. Investig. Drugs, **2002**, 11(10), 1365.

[147] Sheng, W.S.; Hu, S.; Min, X.; Cabral, G.A.; Lokensgard, J.R.; Peterson, P.K. *Glia*, **2005**, *49(2)*, 211.

[148] Panikashvili, D.; Mechoulam, R.; Beni, S.M.; Alexandrovich, A.; Shohami, E. *J. Cereb. Blood Flow Metab.*, **2005**, *25(4)*, 477.

[149] Kim, S.H.; Won, S.J.; Mao, X.O.; Jin, K.; Greenberg, D.A. *J. Pharmacol. Exp. Ther.*, **2005**, *313(1)*, 88.

[150] Van der Stelt, M.; Veldhuis, W.B.; Bar, P.R.; Veldink, G.A.; Vliegenthart, J.F.; Nicolay, K. *J. Neurosi.*, **2001**, *21(17)*, 6475.

[151] Milton, N.G. *Subcell. Biochem.*, **2005**, *38*, 381.

[152] Ramirez, B.G.; Blazquez, C.; Gomez del Pulgar, T.; Guzman, M.; de Ceballos, M.L. *J. Neurosci.*, **2005**, *25(8)*, 1904.

[153] Tashkin, D.P.; Levisman, J.A.; Abbasi, A.S.; Shapiro, B.J.; Ellis, N.M. *Chest*, **1977**, *72(1)*, 20.

[154] Benowitz, N.L.; Jones, T. *Clin. Pharmacol. Ther.*, **1975**, *18*, 287.

[155] Formukong, E.A.; Evans, A.T.; Evans. F.J. *J Pharm Pharmacol* **1989**, *41(10)*, 705.

[156] O'Leary, D.S.; Block, R.I.; Koeppel, J.A.; Flaum, M.; Schultz, S.K.; Andreasen, N.C.; Ponto, L.B.; Watkins, G.L.; Hurtig, R.R.; Hichwa, R.D. *Neuropsychopharmacology*, **2002**, *26(6)*, 802.

[157] Herning, R.I.; Better, W.E.; Tate, K.; Cadet, J.L. *Neurology*, **2005**, *64(3)*, 488.

[158] Szabo, B.; Nordheim, U.; Niederhoffer, N. *J. Pharmacol. Exp. Ther.*, **2001**, *297*, 819.

[159] Huestis, M.A.; Gorelick, D.A.; Heishman, S.J.; Preston, K.L.; Nelson, R.A.; Moolchan, E.T.; Frank. R.A. *Arch. Gen. Psychiatry*, **2001**, *58(4)*, 322.

[160] Lake, K.D.; Compton, D.R.; Varga, K.; Martin, B.R.; Kunos, G. *J. Pharmacol. Exp. Ther.*, **1997**, *281*, 1030.

[161] Wagner, J.A.; Varga, K.; Kunos, G. *J. Mol. Med.*, **1998**, *76(12)*, 824.

[162] Wagner, J.A.; Jarai, Z.; Batkai, S; Kunos, G. *Eur. J. Pharmacol.*, **2001**, *423(2-3)*, 203.

[163] Fride, E.; Shohami, E. *Neuroreport*, **2002**, *13(15)*, 1833.

[164] Williams, C.M.; Kirkham, T.C. *Psychopharmacology*, **1999**, *143(3)*, 315.

[165] Williams, C.M.; Kirkham, T.C. *Physiol. Behav.*, **2002**, *76(2)*, 241.

[166] Shook, J.E.; Burks, T.F. *J. Pharmacol. Exp. Ther.*, **1989**, *249(2)*, 444.

[167] McCallum, R.W.; Soykan, I.; Sridhar, K.R.; Ricci, D.A.; Lange, R.C.; Plankey, M.W. Aliment *Pharmacol. Ther.*, **1999**, *13(1)*, 77.

[168] Coruzzi, G.; Adami, M.; Coppelli, G.; Frati, P.; Soldani, G. *Naunyn Schmiedebergs Arch. Pharmacol.*, **1999**, *360*, 715.

[169] Adami, M.; Frati, P.; Bertini, S.; Kulkarni-Narla, A.; Brown, D.R.; De Caro, G.; Coruzzi, G.; Soldani, G. *Br. J. Pharmacol.*, **2002**, *135*, 1598.

[170] Adami, M.**;** Zamfirova, R.**;** Sotirov, E.**;** Tashev, R.**;** Dobrinova, Y.**;** Todorov, S.**;** Coruzzi, G. *Brain. Res. Bull.*, **2004**, *64(4)*, 357.

[171] Cabral, G. In *Cannabis and Cannabinoids. Pharmacology*, *Toxicology*, *and Therapeutic Potential*. Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *25,* pp. 279-288.

[172] Melamede, R. In *Cannabis and cannabinoids. Pharmacology*, *toxicology*, *and therapeutic potential.* Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *10*, pp. 111-122.

[173] Evans, A.T.; Formukong, E.A.; Evans. F.J. *Biochem. Pharmacol.*, **1987**, *36(12)*, 2035.

[174] Sofia, R.D.; Nalepa, S.D.; Harakal, J.J.; Vassar, V.B. *J. Pharmacol. Exp. Ther.*, **1973**, *186(3)*, 646.

[175] Jan, T.R.; Farraj, A.K.; Harkema, J.R.; Kaminski, N.E. *Toxicol. Appl. Pharmacol.*, **2003**, *188(1)*, 24.

[176] Yuan, M.; Kiertscher, S.M.; Cheng, Q.; Zoumalan, R.; Tashkin, D.P.; Roth, M.D. *J. Neuroimmunol.*, **2002**, *133(1-2)*, 124.

[177] Lancz, G.; Specter, S.; Brown, H.K. *Proc. Soc. Exp. Biol. Med. X.*, **2002**, *196(4)*, 401.

[178] Medveczky, M.M.; Sherwood, T.A.; Klein, T.W.; Friedman, H.; Medveczky, P.G. *BMC Med.*, **2004**, *2(1),* 34.

[179] Mbvundula, E.C.; Bunning, R.A.; Rainsford, K.D. *Biochem. Pharmacol.*, **2005**, *69(4),* 635.

[180] Pate, D.W. In *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential.* Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *2*, pp. 15-26.

[181] Colasanti, B.K. *J. Ocul .Pharmacol*., **1990**, *6*, 259.

[182] Laine, K.; Jarvinen, K.; Jarvinen, T. *Life Sci.*, **2003**, *72(7)*, 837.

[183] Tahir, S.K.; Trogadis, J.E.; Stevens, J.K.; Zimmerman, A.M. *Biochem. Cell. Biol.*, **1992**, *70(10-11)*, 1159.

[184] De Petrocellis, L.; Melck, D.; Palmisano, A.; Bisogno, T.; Laezza, C.; Bifulco, M.; Di Marzo, V. *Proc. Natl. Acad. Sci. USA*, **1998**, *95(14)*, 8375.

[185] Melck, D.; De Petrocellis, L.; Orlando, P.; Bisogno, T.; Laezza, C.; Bifulco, M.; Di Marzo, V. *Endocrinology*, **2000**, *141(1)*, 118.

[186] Galve-Roperh, I.; Sanchez, C.; Cortes, M.L.; del Pulgar, T.G.; Izquierdo, M.; Guzman, M. *Nat. Med.*, **2000**, *6(3)*, 313.

[187] Murphy, L. In *Cannabis and cannabinoids. Pharmacology*, *toxicology*, *and therapeutic potential.* Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *26*, pp. 289-298.

[188] Habayeb, O.M.; Taylor, A.H.; Evans, M.D.; Cooke, M.S.; Taylor, D.J.; Bell, S.C.; Konje, J.C. *J. Clin. Endocrinol. Metab.*, **2004**, *89(11)*, 5482.

[189] Hembree 3d, W.C.; Nahas, G.G.; Zeidenberg, P.; Huang, H.F. *Adv. Biosci.*, **1978**, *22-23*, 429.

[190] Chang, M.C.; Berkery, D.; Schuel, R.; Laychock, S.G.; Zimmerman, A.M.; Zimmerman, S.; Schuel, H. *Mol. Reprod. Dev.*, **1993**, *36*, 507.

[191] Boger, D.L.; Miyauchi, H; Du, W.; Hardouin, C.; Fecik, RA.; Cheng, H.; Hwang, I.; Hedrick, MP.; Leung, D.; Acevedo, O.; Guimaraes, C.R.; Jorgensen, WL.; Cravatt, B.F. *J. Med. Chem.*, **2005**, *48(6)*, 1849.

[192] Rodella, L.F.; Borsani, E.; Rezzani, R.; Ricci, F.; Buffoli, B.; Bianchi, R. *Eur. J. Pharmacol.*, **2005**, *508(1-3)*, 139.

[193] Kathuria, S.; Gaetani, S.; Fegley, D.; Valino, F.; Duranti, A.; Tontini, A.; Mor, M.; Tarzia, G.; La Rana, G.; Calignano, A.; Giustino, A.; Tattoli, M.; Palmery, M.; Cuomo, V.; Piomelli, D. *Nat. Med.*, **2003**, *9(1)*, 76.

[194] Mestre, L.; Correa, F.; Arevalo-Martin, A.; Molina-Holgado, E.; Valenti, M.; Ortar, G.; Di Marzo, V.; Guaza, C. *J. Neurochem.*, **2005**, *92(6)*, 1327.

[195] Ni, X.; Geller, E.B.; Eppihimer, M.J.; Eisenstein, T.K.; Adler, M.W.; Tuma, R.F. *Mult. Scler.*, **2004**, *10(2)*, 158.

[196] Wiley, J.L.; Smith, F.L.; Razdan, R.K.; Dewey, W.L. *Eur. J. Pharmacol.*, **2005**, *510(1-2)*, 59.

[197] Jacobsson, S.O.; Wallin, T.; Fowler, C.J. *J. Pharmacol. Exp. Ther.*, **2001**, *299(3)*, 951.

[198] Domenicali, M.; Ros, J.; Fernandez-Varo, G.; Cejudo-Martin, P.; Crespo, M.; Morales-Ruiz, M.; Briones, A.M.; Campistol, J.M.; Arroyo, V.; Vila, E.; Rodes, J.; Jimenez, W. *Gut.*, **2005**, *54(4)*, 522.

[199] Kishimoto, S.; Muramatsu, M.; Gokoh, M.; Oka, S.; Waku, K.; Sugiura, T. *J. Biochem. (Tokyo)*, **2005**, *137(2)*, 217.

[200] Zuardi, A.W.; Shirakawa, I.; Finkelfarb, E.; Karniol, I.G. *Psychopharmacology*, **1982**, *76(3)*, 245.

[201] Petitet, F.; Jeantaud, B.; Reibaud, M.; Imperato, A.; Dubroeucq. M.C. *Life Sci.*, **1998**, *63(1)*, 1.

[202] Bisogno, T.; Hanus, L.; De Petrocellis, L.; Tchilibon, S.; Ponde, D.E.; Brandi, I.; Moriello, A.S.; Davis, J.B.; Mechoulam, R.; Di Marzo, V. *Br. J. Pharmacol.*, **2001**, *134*, 845.

[203] Mechoulam, R.; Hanus, L. *Chem. Phys. Lipids*, **2002**, *121(1-2)*, 35.

[204] Bornheim, L.M.; Kim, K.Y.; Li, J.; Perotti, B.Y.; Benet, L.Z. *Drug Metab. Dispos.*, **1995**, *23*, 825.

[205] Bornheim, L.M.; Grillo, M.P. *Chem. Res. Toxicol.*, **1998**, *11*, 1209.

[206] Jaeger, W.; Benet, L.Z.; Bornheim. L.M. *Xenobiotica*, **1996**, *26(3)*, 275.

[207] Agurell, S.; Carlsson, S.; Lindgren, J.E.; Ohlsson, A.; Gillespie, H.; Hollister, H. *Experientia*, **1981**, *37*, 1090.

[208] Hunt, C.A.; Jones, R.T.; Herning, R.I.; Bachman. J. *J. Pharmacokinet. Biopharm.*, **1981**, *9(3)*, 245.

[209] Costa, B.; Colleoni, M.; Conti, S.; Parolaro, D.; Franke, C.; Trovato, A.E.; Giagnoni, G. *Naunyn Schmiedebergs Arch. Pharmacol.*, **2004**, *369*, 294.

[210] Zuardi, A.W.; Guimarães, F.S.; Guimarães, V.M.C.; Del Bel, E.A. In *Cannabis and Cannabinoids. Pharmacology*, *Toxicology*, *and Therapeutic Potential*. Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *33*, pp. 359-70.

[211] Karler, R.; Turkanis, S.A. *J. Clin. Pharmacol.*, **1981**, *21(8-9)*, 437.

[212] Consroe, P.; Sandyk, R.; Snider, S.R. *Int. J. Neurosi.*, **1986**, *30*, 277.

[213] Parker, L.A.; Mechoulam, R.; Schlievert, C. *Neuroreport*, **2002**, *13(5)*, 567.

[214] Malfait, A.M.; Gallily, R.; Sumariwalla, P.F.; Malik, A.S.; Andreakos, E.; Mechoulam, R.; Feldmann, M. *Proc. Natl. Acad. Sci. USA*, **2000**, *97(17)*, 9561.

[215] Sacerdote, P.; Martucci, C.; Vaccani, A.; Bariselli, F.; Panerai, A.E.; Colombo, A.; Parolaro, D.; Massi, P. *J. Neuroimmunol.*, **2005**, *159(1-2)*, 97.

[216] Colasanti, B.K.; Brown, R.E.; Craig, C.R. *Gen. Pharmacol.*, **1984**, *15*, 479.

[217] Karler, R.; Turkanis, S.A. *NIDA. Res. Monogr.*, **1987**, *79*, 96.

[218] Burstein, S.H.; Audette, C.A.; Doyle, S.A.; Hull, K.; Hunter, S.A.; Latham, V.; *J. Pharmacol. Exp. Ther.*, **1989**, *251*, 531.

[219] Burstein, S.H; *Pharmacol. Ther.*, **1999**, *82*, 87.

[220] Doyle, S.A.; Burstein, S.H.; Dewey, W.L.; Welch, S.P. *Agents Actions*, **1990**, *31(1-2)*, 157.

[221] Burstein, S.; Hunter, S.A.; Latham, V.; Renzulli, L.; *Experientia*, **1987**, *43*, 402.

[222] Liu, J.; Li, H.; Burstein, S.H.; Zurier, R.B.; Chen, J.D. *Mol. Pharmacol.*, **2003**, *63(5)*, 983.
[223] Karst, M.; Salim, K.; Burstein, S.; Conrad, I.; Hoy, L.; Schneider, U. *JAMA*, **2003**, *290(13)*, 1757.
[224] Pertwee, R.G. *Life Sci.*, **2005**, *76*, 1307.
[225] Schlicker, E.; Kathmann, M. *Pharmacological Sciences*, **2001**, *22 (11)*, 565.
[226] British Medical Association. *Therapeutic uses of cannabis*. Harwood Academic Publishers, Amsterdam, **1997**.
[227] Dansak, D.A. In Cannabis in medical practice, A legal, historical and pharmacological overview of the therapeutic use of marijuana. Mathre, M.L., Ed.; McFarland & Co: Jefferson/NC, **1997;** pp. 69-83.
[228] Plasse, T.F.; Gorter, R.W.; Krasnow, S.H.; Lane, M.; Shepard, K.V.; Wadleigh. R.G. *Pharmacol. Biochem. Behav.*, **1991**, *40(3)*, 695.
[229] Clifford, D.B. *Ann. Neurol.*, **1983**, *13*, 669.
[230] Noyes, R.; Baram. D.A.; *Compreh. Psychiatr.*, **1974**, *15*, 531.
[231] Müller-Vahl, K.R.; Kolbe, H.; Dengler. R. *Nervenarzt*, **1997**, *68*, 985.
[232] Volicer, L.; Stelly, M.; Morris, J.; McLaughlin, J.; Volicer, B.J. *Int. J. Geriatr. Psychiatry*, **1997**, *12(9)*, 913.
[233] Hepler, R. S.; Frank, I.M. *JAMA*, **1971**, *217*, 1392.
[234] Chan, P.C.; Sills, R.C.; Braun, A.G.; Haseman, J.K.; Bucher, J.R. *Fundam. Appl. Toxicol.*, **1996**, *30*, 109.
[235] Ware, M.A.; Adams, H.; Guy, G.W. *IJCP*, **2005**, *59 (3)*, 291.
[236] de Jong, B.C.; Prentiss, D.; McFarland, W.; Machekano, R.; Israelski, D.M. *J. Acquir. Immune. Defic. Syndr.*, **2005,** *38(1),* 43.
[237] Grinspoon, L.; Bakalar. J.B. *Marihuana*, *the forbidden medicine*. Yale University Press, New Haven, **1993.**
[238] Grotenhermen, F. In *Cannabis and cannabinoids. Pharmacology*, *toxicology*, *and therapeutic potential.*, Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *11*, pp. 123-42.
[239] Mathre, M.L. Cannabis in medical practice, A legal, historical and pharmacological overview of the therapeutic use of marijuana. McFarland & Co., Jefferson, NC, **1997**.
[240] Mechoulam, R. *Cannabinoids as therapeutic agents*. CRC Press: Boca Raton, **1986**.
[241] Beal, J.E.; Olson, R.; Laubenstein, L.; Morales, J.O.; Bellman, P.; Yangco, B.; Lefkowitz, L. *J. Pain. Symptom. Manage*, **1995**, *10*, 89.
[242] Beal, J.E.; Olson, R.; Lefkowitz, L.; Laubenstein, L.; Bellman, P.; Yangco, B.; Morales, J.O.; Murphy, R.; Powderly, W.; Plasse, T.F.; Mosdell, K.W.; Shepard, K.V. *J. Pain Symptom. Manage*, **1997**, *14*, 7.
[243] Musty, R.E.; Rossi, I. *J. Cannabis. Ther.*, **2001**, *1(1),* 29.
[244] Soderpalm, A.H.; Schuster, A.; de Wit, H. *Pharmacol. Biochem. Behav.*, **2001**, *69(3-4)*, 343.
[245] Gonzalez-Rosales, F.; Walsh, D. *J. Pain Symptom Manage*, **1997**, *14(5),* 311.
[246] Kwiatkowska, M.; Parker, L.A.; Burton, P.; Mechoulam, R. *Psychopharmacology (Berl)*, **2004**, *174(2),* 254.
[247] Jatoi, A.; Windschitl, H.E.; Loprinzi, C.L.; Sloan, J.A.; Dakhil, S.R.; Mailliard, J.A.; Pundaleeka, S.; Kardinal, C.G.; Fitch, T.R.; Krook, J.E.; Novotny, P.J.; Christensen, B. *J. Clin. Oncol.*, **2002**, *20(2)*, 567.
[248] Haney, M.; Rabkin, J.; Gunderson, E.; Foltin, R.W. *Psychopharmacology (Berl)*, **2005**, [Epub ahead of print].
[249] Elsner, F.; Radbruch, L.; Sabatowski, R. *Schmerz*, **2001**, *15(3)*, 200.
[250] Holdcroft, A.; Smith, M.; Jacklin, A.; Hodgson, H.; Smith, B.; Newton, M.; Evans, F. *Anaesthesia*, **1997**, *52(5)*, 483.
[251] Maurer, M.; Henn, V.; Dittrich, A.; Hofmann, A. *Eur. Arch. Psychiatry. Neurol. Sci.*, **1990**, *240(1)*, 1.
[252] Notcutt, W.G.; Price, M.; Chapman, G. *Pharmac. Sci.*, **1997**, *11*, 551.
[253] Noyes, R. Jr.; Brunk, S.F.; Avery, D.A.H.; Canter, A.C. *Clin. Pharmacol. Ther.*, **1975**, 18*(1)*, 84.
[254] Noyes, R. Jr.; Brunk, S.F.; Baram, D.A.; Canter, A. *J. Clin. Pharmacol.*, **1975**, 15*(2-3)*, 139.
[255] Petro, D.J. *Psychosomatics.*, **1980**, *21(1)*, 81.
[256] Campbell, F.A.; Tramer, M.R.; Carroll, D.; Reynolds, D.J., Moore, R.A.; McQuay, H.J. *BMJ*, **2001**, *323(7303),* 13.
[257] Kalso, E. *BMJ*, **2001**, *323(7303)*, 2.
[258] Johanek, L.M.; Simone, D.A. *Pain*, **2004**, *109(3),* 432.
[259] Berman, J.S.; Symonds, C.; Birch, R. *Pain*, **2004**, *112(3),* 299.
[260] Svendsen, K.B.; Jensen, T.S.; Bach, F.W. *BMJ*, **2004**, *329(7460)*, 253.
[261] Zajicek, J.; Fox, P.; Sanders, H.; Wright, D.; Vickery, J.; Nunn, A.; Thompson, A. *Lancet*, **2003**, *362(9395)*, 1517.
[262] Wade, D.T.; Robson, P.; House, H.; Makela, P.; Aram, J. *Clin. Rehabil.*, **2003**, *17*, 18.
[263] Notcutt, W.; Price, M.; Miller, R.; Newport, S.; Phillips, C.; Simmons, S.; Sansom, C. *Anaesthesia*, **2004**, 59*(5),* 440.
[264] Attal, N.; Brasseur, L; Guirimand, D.; Clermond-Gnamien, S.; Atlami, S.; Bouhassira, D. *Eur. J. Pain*, **2004**, *8(2)*, 173.
[265] Cichewicz, D.L.; McCarthy, E.A. *J. Pharmacol. Exp. Ther.*, **2003**, *304*, 1010.
[266] Finn, D.P.; Beckett, S.R.; Roe, C.H.; Madjd, A.; Fone, K.C.; Kendall, D.A.; Marsden, C.A.; Chapman, V. *Eur. J. Neurosi.*, **2004**, *19(3),* 678.
[267] Welch, S.P.; Eads, M. *Brain Res.*, **1999**, *848(1-2)*, 183.
[268] Brenneisen, R.; Egli, A.; Elsohly, M.A.; Henn, V.; Spiess, Y. *Int. J. Clin. Pharmacol. Ther.*, **1996**, *34*,446.
[269] Martyn, C.N.; Illis, L.S.; Thom, J. *Lancet*, **1995**, *345(8949)*, 579.
[270] Meinck, H.M.; Schonle, P.W.; Conrad, B. *J. Neurol.*, **1989**, *236(2)*, 120.
[271] Petro, D.J.; Ellenberger, C. Jr.; *J. Clin. Pharmacol.*, **1981**, *21(8-9 Suppl)*, 413.
[272] Ungerleider, J.T.; Andyrsiak, T.; Fairbanks, L.; Ellison, G.W.; Myers, L.W. *Adv. Alcohol Subst. Abuse.*, **1987**, *7(1)*, 39.
[273] Brady, C.M.; DasGupta, R.; Dalton, C.; Wiseman, O.J.; Berkley, K.J.; Fowler, C.J. *Mult. Scler.*, **2004**, 10*(4),* 425.
[274] Killestein, J.; Hoogervorst, E.L.; Reif, M.; Kalkers, N.F.; Van Loenen, A.C.; Staats, P.G.; Gorter, R.W.; Uitdehaag, B.M.; Polman, C.H. *Neurology*, **2002**, *58(9)*, 1404.
[275] Vaney, C.; Heinzel-Gutenbrunner, M.; Jobin, P.; Tschopp, F.; Gattlen, B.; Hagen, U.; Schnelle, M.; Reif, M. *Mult. Scler.*, **2004**, *10(4),* 417.
[276] Wade, D.T.; Makela, P.; Robson, P.; House, H.; Bateman, C. *Mult. Scler.*, **2004**, *10(4),* 434.
[277] Zajicek, J. *Mult.Scler*., **2004**, *10 (suppl 2)*, 115.
[278] Shakespeare, D.T.; Boggild, M.; Young, C. *Cochrane Database Syst. Rev.*, **2000**, *(4),* CD001332.
[279] Fox, S.H.; Kellett, M.; Moore, A.P.; Crossman, A.R.; Brotchie, J.M. *Mov. Disord.*, **2002**, *17(1)*, 145.
[280] Hemming, M.; Yellowlees, P.M. *J. Psychopharmacol*., **1993**, *7*, 389.
[281] Müller-Vahl, K.R.; Schneider, U.; Koblenz, A.; Jobges, M.; Kolbe, H.; Daldrup, T.; Emrich, H.M. *Pharmacopsychiatry*, **2002**, *35(2)*, 57.
[282] Müller-Vahl, K.R.; Schneider, U.; Kolbe, H.; Emrich, H.M. *Am. J. Psychiatry*, **1999**, *156(3)*, 495.
[283] Sandyk, R.; Awerbuch, G. *J. Clin. Psychopharmacol.*, **1998**, *8*, 844.
[284] Sieradzan, K.A.; Fox, S.H.; Hill, M.; Dick, J.P.; Crossman, A.R.; Brotchie, J.M. *Neurology*, **2001**, *57(11)*, 2108.
[285] Carroll, C.B.; Bain, P.G.; Teare, L.; Liu, X.; Joint, C.; Wroath, C.; Parkin, S.G.; Fox, P.; Wright, D.; Hobart, J.; Zajicek, J.P. *Neurology*, **2004,** *63(7),* 1245.
[286] Crawford, W.J.; Merritt, J.C. *Int. J. Clin. Pharmacol. Biopharm.*, **1979**, *17*, 191.
[287] Hepler, R.S.; Petrus, R.J. In *The therapeutic potential of marihuana*. Cohen, S.; Stillman, R.C.; Eds.; Plenum Medical Book: New York NY, **1976**; pp. 63-75.
[288] Merritt, J.C.; Crawford, W.J.; Alexander, P.C.; Anduze, A.L.; Gelbart, S.S. *Ophthalmology*, **1980**, *87(3)*, 222.
[289] Merritt, J.C.; Olsen, J.L.; Armstrong, J.R.; McKinnon, S.M. *J. Pharm. Pharmacol.*, **1981**, *33(1)*, 40.
[290] Hartley, J.P.; Nogrady, S.G.; Seaton, A. *Br. J. Clin. Pharmacol.*, **1978**, *5(6)*, 523.
[291] Tashkin, D.P.; Shapiro, B.J.; Frank, I.M. *Am. Rev. Respir. Dis.*, **1974**, *109(4)*, 420.
[292] Williams, S.J.; Hartley, J.P.; Graham, J.D. *Thorax*, **1976**, *31(6)*, 720.
[293] Yoshihara, S.; Morimoto, H.; Yamada, Y.; Abe, T.; Arisaka, O. *Am. J. Respir. Crit. Care Med.*, **2004**, *170(9),* 941.
[294] Glass, R.M.; Uhlenhuth, E.H.; Hartel, F.W.; Schuster, C.R.; Fischman, M.W. *J. Clin. Pharmacol.*, **1981**, *21(8-9 Suppl)*, 383.
[295] Glass, R.M.; Uhlenhuth, E.H.; Hartel, F.W.; Schuster, C.R.; Fischman, M.W. *Psychopharmacology (Berl)*, **1980**, *71(2),* 137.

[296] Schnelle, M.; Grotenhermen, F.; Reif, M.; Gorter, R.W. *Forsch Komplementarmed* [Res Complementary Med], **1999**, *28 (Sup*pl *3)*, 36.
[297] Gordon, E.; Devinsky, O. *Epilepsia*, **2001**, *42(10)*, 1266.
[298] Gilson, I.; Busalacchi, M. *Lancet*, **1998**, *351(9098)*, 267.
[299] Grinspoon, L.; Bakalar, J.B. *J. Psychoactive. Drugs*., **1998**, *30(2)*, 171.
[300] Mikuriya, T.H. *Med. Times*, **1970**, *98(4)*, 187.
[301] Arevalo-Martin, A.; Vela, J.M.; Molina-Holgado, E.; Borrell, J.; Guaza, C. *J. Neurosi.*, **2003**, *23*, 2511.
[302] Croxford, J.L.; Miller, S.D. *J. Clin. Invest.*, **2003**, *111*, 1231.
[303] Raman, C.; McAllister, SD.; Rizvi, G.; Patel, S.G.; Moore, D.H.; Abood, M.E. *Amyotroph. Lateral Scler. Other Motor Neuron. Disord.*, **2004**, *5(1),* 33.
[304] Casanova, M.L.; Blazquez, C.; Martinez-Palacio, J.; Villanueva, C.; Fernandez-Acenero, M.J.; Huffman, J.W.; Jorcano, J.L.; Guzman, M. *J. Clin. Invest.*, **2003**, *111*, 43.
[305] Ligresti, A.; Bisogno, T.; Matias, I.; De Petrocellis, L.; Cascio, M.G.; Cosenza, V.; D'argenio, G.; Scaglione, G.; Bifulco, M.; Sorrentini, I.; Di Marzo, V. *Gastroenterology*, **2003**, *125(3),* 677.
[306] Sarfaraz, S.; Afaq, F.; Adhami, V.M.; Mukhtar, H. *Cancer Res.*, **2005**, *65(5)*, 1635.
[307] Guzman, M.; Sanchez, C.; Galve-Roperh, I. *J. Mol. Med.*, **2001**, *78(11)*, 613.
[308] Blazquez, C.; Casanova, M.L.; Planas, A.; Del Pulgar, T.G.; Villanueva, C.; Fernandez-Acenero, M.J.; Aragones, J.; Huffman, J.W.; Jorcano, J.L.; Guzman, M. *FASEB. J.*, **2003**, *17*, 529.
[309] McKallip, R.J.; Nagarkatti, M.; Nagarkatti, P.S. *J. Immunol.*, **2005**, *174(6)*, 3281.
[310] Hart, S.; Fischer, O.M.; Ullrich, A. *Cancer Res.*, **2004**, *64(6)*, 1943.
[311] Ralevic, V.; Kendall, D.A. *Eur. J. Pharmacol*., **2001**, *418(1-2)*, 117.
[312] Wagner, J.A.; Hu, K.; Karcher, J.; Bauersachs, J.; Schafer, A.; Laser, M.; Han, H.; Ertl, G. *Br. J. Pharmacol.*, **2003**, *138(7)*, 1251.
[313] Izzo, A.A.; Pinto, L.; Borrelli, F.; Capasso, R.; Mascolo, N.; Capasso. F. *Br. J. Pharmacol.*, **2000**, *129(8)*, 1627.
[314] Carley, D.W.; Paviovic, S.; Janelidze, M.; Radulovacki, M. *Sleep*, **2002**, *25*, 391.
[315] Adriani, W**.;** Caprioli, A**.;** Granstrem, O**.;** Carli, M**.;** Laviola, G. *Neurosi. Biobehav. Rev.*, **2003**, *27(7)*, 639.
[316] Zuardi, A.W.; Cosme, R.A.; Graeff, F.G.; Guimarães, F.S. *J. Psychopharmacol.*, **1993**, *7*, 82.
[317] Consroe, P.; Laguna, J.; Allender, J.; Snider, S.; Stern, L.; Sandyk, R.; Kennedy, K.; Schram, K. *Biochemistry and Behavior*, **1991**, *40(3)*, 701
[318] Cunha, J.M.; Carlini, E.A.; Pereira, A.E.; Ramos, O.L.; Pimentel, C.; Gagliardi, R.; Sanvito, WL.; Lander, N.; Mechoulam, R. *Pharmacology*, **1980**, *21(3)*, 175.
[319] Karniol, I.G.; Carlini, EA. *Psychopharmacologia*, **1973**, *33(1)*, 53.
[320] Karniol, I.G.; Shirakawa, I.; Kasinski, N.; Pfeferman, A.; Carlini, E.A. *Eur. J. Pharmacol.*, **1974**, *28(1)*, 172.
[321] Lipton, S.A.; Rosenberg, P.A. *N. Engl. J. Med.*, **1994**, *330*, 613.
[322] Lavie, G.; Teichner, A.; Shohami, E.; Ovadia, H.; Leker, R.R. *Brain Research*, **2001**, *901(1-2)*, 195.
[323] Zalish, M.; Lavie, V. *Vision Research*, **2003**, *43(3)*, 237.
[324] Achiron, A.; Miron, S.; Lavie, V.; Margalit, R.; Biegon, A. *J. Neuroimmunol.*, **2000**, *102(1)*, 26.
[325] Knoller, N.; Levi, L.; Shoshan, I.; Reichenthal, E.; Razon, N.; Rappaport, Z.H.; Biegon, A. *Crit. Care. Med.*, **2002**, *30(3)*, 548.
[326] Raja, P.V.; Blumenthal, J.A.; Doraiswamy, P.M. *CNS Spectr.*, **2004**, 9*(10)*, 763.
[327] Kadoi, Y.; Hinohara, H.; Kunimoto, F.; Kuwano, H.; Saito, S.; Goto, F. *Br. J. Anaesth.*, **2005**, *94(5)*, 563.
[328] Di Marzo, V.; Hill, M.P.; Bisogno, T.; Crossman, A.R.; Brotchie. J.M. *FASEB. J.*, **2000**, 14*(10)*, 1432.
[329] Müller-Vahl, K.R.; Schneider, U.; Emrich, H.M. *Mov. Disord.*, **1999**, *14(6)*, 1038.
[330] Vacca, G.; Serra, S.; Brunetti, G.; Carai, M.A.; Gessa, G.L.; Colombo, G. *Eur. J. Pharmacol.*, **2002**, *445(1-2)*, 55.
[331] Solinas, M.; Panlilio, L.V.; Antoniou, K.; Pappas, L.A.; Goldberg, S.R. *J. Pharmacol. Exp. Ther.*, **2003**, *306(1);* 93.
[332] Batkai, S.; Jarai, Z.; Wagner, J.A.; Goparaju, S.K.; Varga, K.; Liu, J.; Wang, L.; Mirshahi, F.; Khanolkar, A.D.; Makriyannis, A.; Urbaschek, R.; Garcia, N Jr.; Sanyal, A.J.; Kunos, G. *Nat. Med.*, **2001**, *7(7)*, 827.
[333] Vinod, K.Y.; Arango, V.; Xie, S.; Kassir, S.A.; Mann, J.J.; Cooper, T.B.; Hungund, B.L. *Biol. Psychiatry*, **2005**, *57(5)*, 480.
[334] Van Gaal, L.F.; Rissanen, A.M.; Scheen, A.J.; Ziegler, O.; Rossner, S.; RIO-Europe Study Group. *Lancet*, **2005**, *365(9468)*, 1389.
[335] Black, S.C. Curr Opin Investig Drugs. **2004**, 5(4), 389.
[336] Fernandez, J.R.; Allison, D.B. *Curr. Opin. Investig. Drugs*, **2004**, *5(4)*, 430.
[337] Russo, E.; Mathre, M.L.; Byrne, A.; Velin, R.; Bach, P.J.; Sanchez-Ramos, J.; Kirlin, K.A. *J. Cannabis. Ther.*, **2002**, *2(1)*, 3.
[338] Thompson, G.R.; Rosenkrantz, H.; Schaeppi, U.H.; Braude, M.C. *Toxicol. Appl. Pharmacol.*, **1973**, *25(3)*, 363.
[339] Bachs, L.; Morland, H. *Forensic. Sci. Int.*, **2001**, *124*, 200.
[340] Mittleman, M.A.; Lewis, R.A.; Maclure, M.; Sherwood, J.B.; Muller, J.E. *Circulation*, **2001**, *103(23)*, 2805.
[341] Pope, H.G. Jr.; Gruber, A.J.; Hudson, J.I.; Huestis, M.A.; Yurgelun-Todd, D. *Arch. Gen. Psychiatry*, **2001**, *58(10)*, 909.
[342] Pope, H.J. *JAMA*, **2002**, *287(9)*, 1172.
[343] Solowij, N.; Stephens, R.S.; Roffman, R.A.; Babor, T.; Kadden, R.; Miller, M.; Christiansen, K.; McRee, B.; Vendetti, J. *JAMA*, **2002**, *287(9)*, 1123.
[344] Lyketsos, C.G.; Garrett, E.; Liang, K.Y.; Anthony, J.C. *Am. J. Epidemiol.*, **1999**, *149(9)*, 794.
[345] Pope, H.G.; Gruber, A.J.; Hudson, J.I.; Gohane, G.; Huestis, M.A.; Yurgelun-Todd, D. *Drug Alcohol Depend.*, **2003**, *69(3)*, 303.
[346] Fried, P.A.; Watkinson, B.; Gray, R. *Neurotoxicol. Teratol.*, **2005**, *27(2)*, 231.
[347] Lyons, M.J.; Bar, J.L.; Panizzon, M.S.; Toomey, R.; Eisen, S.; Xian, H.; Tsuang, M.T. *Psychol. Med.*, **2004**, *34(7)*, 1239.
[348] Grant, I.; Gonzalez, R.; Carey, C.L.; Natarajan, L.; Wolfson, T. *J. Int. Neuropsychol. Soc.*, **2003**, *9(5),* 679.
[349] Fried, P.A.; Watkinson, B.; Gray, R. *Neurotoxicol. Teratol.*, **1998**, *20(3)*, 293.
[350] Nunez, L.A.; Gurpegui, M. *Acta. Psychiatr. Scand.*, **2002**, *105(3)*, 173.
[351] Arseneault, L.; Cannon, M.; Witton, J.; Murray, R.M. *Br. J. Psychiatry*, **2004**, *184*, 110.
[352] Lynskey, M.T.; Glowinski, A.L.; Todorov, A.A.; Bucholz, K.K.; Madden, P.A.; Nelson, E.C.; Statham, D.J.; Martin, N.G.; Heath, A.C. *Arch. Gen. Psychiatry*, **2004**, *61(10)*, 1026.
[353] Musty, R.E.; Kaback, L. *Life Sci.*, **1995**, *56(23-24)*, 2151.
[354] Julien, B.; Grenard, P.; Teixeira-Clerc, F.; Van Nhieu, J.T.; Li, L.; Karsak, M.; Zimmer, A.; Mallat, A.; Lotersztajn, S. *Gastroenterology*, **2005**, *128(3)*, 742.
[355] Tashkin, D.P. In *Cannabis and Cannabinoids. Pharmacology*, *Toxicology*, *and Therapeutic Potential*. Grotenhermen, F.; Russo, E.; Eds.; Haworth Press: Binghamton NY, **2002**; Vol. *29*, pp. 325-335.
[356] Romero, J.; Garcia-Palomero, E; Castro, J.G.; Garcia-Gil, L.; Ramos, J.A.; Fernandez-Ruiz, J.J. *Brain Res. Mol. Brain Res.*, **1997**, *46(1-2)*, 100.
[357] Jones, R.T.; Benowitz, N.; Bachman, J. *Ann. N. Y. Acad. Sci.*, **1976**, *282*, 221.
[358] Stefanis, C. *NIDA Res. Monogr.*, **1978**, 19, 149.
[359] Bass, C.E.; Martin, B.R. *Drug Alcohol Depend.*, **2000**, *60*, 113.
[360] Luthra, Y.K.; Esber, H.J.; Lariviere, D.M.; Rosenkrantz, H. *J. Immunopharmacol.*, **1980**, *2(2)*, 245.
[361] Miczek, K.A.; Dixit, B.N. *Psychopharmacology (Berl)*, **1980**, *67(2)*, 195.
[362] Smith, C.G.; Almirez, R.G.; Berenberg, J.; Asch, R.H. *Science* **1983**, *219(4591)*, 1453.
[363] Di Marzo, V.; Berrendero, F.; Bisogno, T.; Gonzalez, S.; Cavaliere, P.; Romero, J.; Cebeira, M.; Ramos, J.A.; Fernandez-Ruiz, J.J. *J. Neurochem.*, **2000**, *74(4)*, 1627.
[364] Rubino, T.; Vigano, D.; Massi, P.; Parolaro, D. *J. Neurochem.*, **2000**, *75(5)*, 2080.
[365] Abood, M.E.; Sauss, C.; Fan, F.; Tilton, C.L.; Martin, B.R. *Pharmacol. Biochem. Behav.*, **1993**, *46*, 575.
[366] Rubino, T.; Vigano, D.; Costa, B.; Colleoni, M.; Parolaro, D. *J. Neurochem.*, **2000**, *75(6)*, 2478.
[367] Costa, B.; Parolaro, D.; Colleoni, M. *Eur. J. Pharmacol*., **1996**, *313*, 17.
[368] Hunt, C.A.; Jones, R.T. *J. Pharmacol. Exp. Ther.*, **1980**, *215(1)*, 35.

[369] Georgotas, A.; Zeidenberg, P. *Compr. Psychiatry*, **1979**, *20(5)*, 427.
[370] Anthony, J.C.; Warner, L.A.; Kessler, R.C. *Experimental and Clin. Psychopharmacol.*, **1994**, *2*, 244.
[371] Kleiber, D.; Soellner, R.; Tossmann, P. Cannabiskonsum in der Bundesrepublik Deutschland, Entwicklungstendenzen, Konsummuster und Einflußfaktoren. Federal Ministry of Health, Bonn, **1997**.
[372] Roques, B. Problemes posées par la dangerosité des drogues. Rapport du professeur Bernhard Roques au Secrétaire d'Etat à la Santé. Paris, **1998**.
[373] Calhoun, S.R.; Galloway, G.P.; Smith, D.E. *J Psychoactive Drugs* **1998**, *30*, 187.
[374] Boyd, S.T.; Fremming, B.A. *Ann. Pharmacother.*, **2005**, *39(4)*, 684.
[375] De Vry, J.; Schreiber, R.; Eckel, G.; Jentzsch, K.R. *Eur. J. Pharmacol.*, **2004**, *483(1)*, 55.
[376] Navarro, M.; Hernandez, E.; Munoz, RM.; del Arco, I.; Villanua, M.A.; Carrera, M.R.; Rodriguez de Fonseca, F. *Neuroreport*, **1997**, *8*, 491.
[377] McLaughlin, P.J.; Winston, K.M.; Limebeer, C.L.; Parker, L.A.; Makriyannis, A.; Salamone, J.D. *Psychopharmacology (Berl)*, **2005,** *180(2)*, 286.
[378] van Oosten, B.W.; Killestein, J.; Mathus-Vliegen, E.M.; Polman, C.H. *Mult. Scler.*, **2004**, *10(3)*, 330.
[379] Pryor, G.T.; Husain, S.; Mitoma, C. *Ann. N. Y. Acad. Sci.*, **1976**, *281*, 171.
[380] Kosel, B.W.; Aweeka, F.T.; Benowitz, N.L.; Shade, S.B.; Hilton, J.F.; Lizak, P.S.; Abrams, D.I. *AIDS*, **2002**, *16(4)*, 543.
[381] Zullino, D.F.; Delessert, D.; Eap, C.B.; Preisig, M.; Baumann, P. *Int. Clin. Psychopharmacol.*, **2002**, *17(3)*, 141.
[382] Hollister, L.E. In *Marihuana and medicine*. Nahas, G.; Sutin, K.M.; Harvey, D.J.; Agurell, S.; Eds.; Humana Press: Totowa NJ, **1999**; Vol. *19*, pp. 273-7.
[383] Sutin, K.M.; Nahas, G.G. . In *Marihuana and medicine*. Nahas, G.; Sutin, K.M.; Harvey, D.J.; Agurell. S.; Eds.; Humana Press: Totowa NJ, **1999**; Vol. *18*, pp. 253-71.
[384] Lane, M.; Vogel, C.L.; Ferguson, J.; Krasnow, S.; Saiers, J.L.; Hamm, J.; Salva, K.; Wiernik, P.H.; Holroyde, C.P.; Hammill, S. *J. Pain. Symptom Manage*, **1991**, *6(6)*, 352.
[385] Brody, S.; Preut, R. *Pharmacol. Biochem. Behav.*, **2002**, *72*, 811.
[386] Koe, B.K.; Milne, G.M.; Weissman, A.; Johnson, M.R.; Melvin. L.S. *Eur. J. Pharmacol.*, **1985**, *109(2)*, 201.
[387] Moss, D.E.; Manderscheid, P.Z.; Montgomery, S.P.; Norman, A.B.; Sanberg, P.R. *Life Sci.*, **1989**, *44(21)*, 1521.
[388] Cichewicz, D.L., Welch, S.P. *J. Pharmacol. Exp. Ther.*, **2003**, *305*, 812.
[389] Pryce, G.; Giovannoni, G.; Baker, D. *Neurosci. Lett.*, **2003**, *341(2),* 164.
[390] Perez-Reyes, M.; Burstein, S.H.; White, W.R.; McDonald, S.A.; Hicks. R.E. *Life Sci.*, **1991**, *48(6)*, 507.
[391] Bonz, A.; Laser, M.; Kullmer, S.; Kniesch, S.; Babin-Ebell, J.; Popp, V.; Ertl, G.; Wagner; J.A. *J. Cardiovasc. Pharmacol.*, **2003**, *41*, 657.
[392] Green, K.; Kearse, E.C.; McIntyre, O.L. *Ophthalmic. Res.*, **2001**, *33(4)*, 217.
[393] Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.*, **1998**, *35*, 199.
[394] Fowler, C.J. Trends Pharmacol. Sci., **2004**, 25(2), 59.