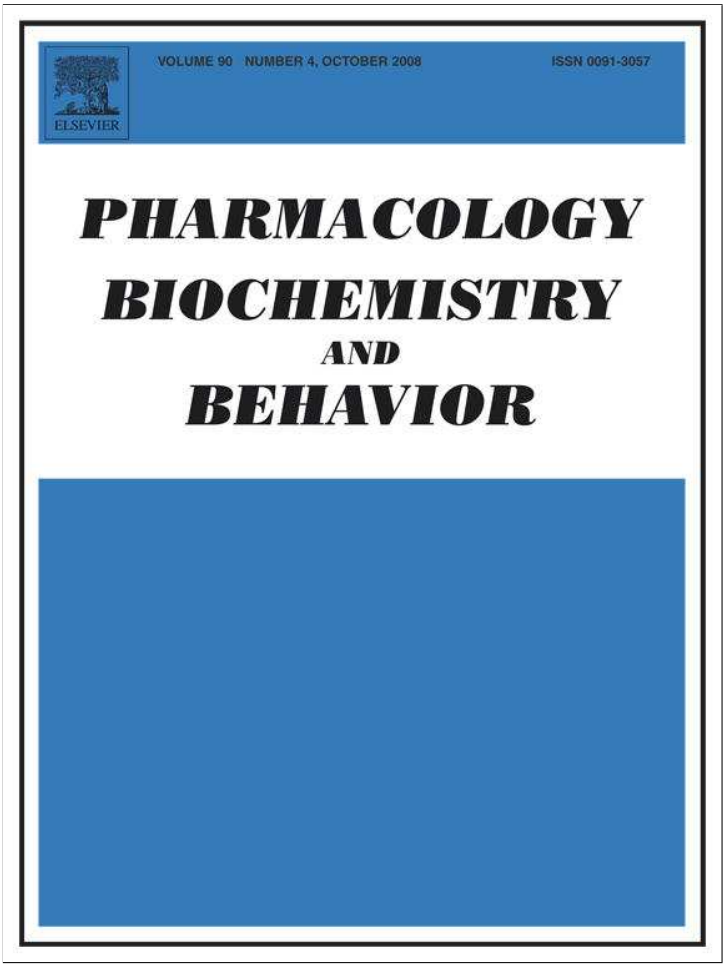

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Review

Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures — A short review

Ivana Svíženská [a,*], Petr Dubový [a], Alexandra Šulcová [b]

[a] Department of Anatomy, Division of Neuroanatomy, Brno, Czech Republic
[b] Department of Pharmacology Faculty of Medicine, Brno, Czech Republic

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ABSTRACT

In the last 25 years data has grown exponentially dealing with the discovery of the endocannabinoid system consisting of specific cannabinoid receptors, their endogenous ligands, and enzymatic systems of their biosynthesis and degradation. Progress is being made in the development of novel agonists and antagonists with receptor subtype selectivity which should help in providing a greater understanding of the physiological role of the endocannabinoid system and perhaps also in a broad number of pathologies. This could lead to advances with important therapeutic potential of drugs modulating activity of endocannabinoid system as hypnotics, analgesics, antiemetics, antiasthmatics, antihypertensives, immunomodulatory drugs, antiphlogistics, neuroprotective agents, antiepileptics, agents influencing glaucoma, spasticity and other "movement disorders", eating disorders, alcohol withdrawal, hepatic fibrosis, bone growth, and atherosclerosis. The aim of this review is to highlight distribution of the CB1 and CB2 receptor subtypes in the nervous system and functional involvement of their specific ligands.

Contents

1. Introduction

Cannabinoids are the terpenophenolic constituents of the hemp plant (*Cannabis sativa*) that has been used for over 4000 years as a recreational drug due to its mind-altering effects. Marijuana, which is made from the dried leaves and tops of the plant, has lower cannabinoid content than hashish, which is a preparation from the dried resin secreted by the plant. The primary psychoactive constituents of cannabis, Δ8-tetrahydrocannabinol (Δ8-THC) and Δ9-THC, were isolated in 1964 (Gaoni and Mechoulam, 1964). Δ9-THC is more prevalent in marijuana and more potent in vivo than Δ8-THC, and thus most of the psychoactivity has been attributed to Δ9-THC (Pertwee, 1988). Δ9-THC is rapidly absorbed and converted in the lungs and liver into a centrally active metabolite, 11-hydroxy-Δ9-THC (Abood and Martin, 1992).

* Corresponding author. Department of Anatomy, Division of Neuroanatomy, Faculty of Medicine, Masaryk University, Kamenice 3, CZ-625 00 Brno, Czech Republic. Tel.: +420 549497543; fax: +420 549491320.
E-mail address: isvizen@med.muni.cz (I. Svíženská).

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The cannabinoids have been shown to produce a unique syndrome of effects on the behaviour of humans and animals that include disruption of short-term memory, cognitive impairments, a sense of time dilation, mood alterations, enhanced body awareness, a reduced ability to focus attention and to filter out irrelevant information, discoordination, and sleepiness (Block et al., 1992; Chait and Perry, 1994; Court, 1998; Heishman et al., 1997).

Human users as well as laboratory animals exhibit both tolerance and dependence following chronic administration of cannabinoids and withdrawal symptoms (nervousness, tension, restlessness, sleep disturbance and anxiety) upon drug cessation (Lichtman and Martin, 2005). A clear-cut abstinence syndrome has been however rarely reported, presumably because of the long life of cannabinoids, which precludes the emergence of abrupt abstinence symptoms. Cannabinoid pharmacokinetic processes which are dynamic, may change distribution over time, be affected by routes of administration, the frequency and magnitude of drug exposure, diverse from different drug formulations and concentrations, are also dependent on poor or extensive type of metabolism (Huestis, 2007). In mice made tolerant to Δ9-THC, however, administration of the selective cannabinoid CB1 receptor antagonist SR141716A after the last Δ9-THC injection promptly precipitated a profound withdrawal syndrome (Cook et al., 1998). Typical withdrawal behaviour in rats became obvious as expressed in an increase in paw tremors and head shakes that was accompanied by a decrease in such normal behaviour as grooming and scratching.

Cannabis sativa was for a longer time reported as the only abused drug which is not self-administered by laboratory animals. However, recently this animal model of dependence showed that the self-administration of cannabinoid receptor agonists is to some extent comparable to those for cocaine and amphetamines in monkeys (Justinová et al., 2003, 2004, 2005a,b; Tanda et al., 2000) and with the existence of strain and sex differences also in laboratory rodents (Fattore et al., 2001, 2007). Moreover, neuroplastic changes are present in the dopaminergic brain reward pathway (ventral tegmental area — accumbens nucleus) and caused by repeated intake of cannabis and other drugs of abuse (Castle and Murray, 2004).

Chronic exposure to cannabis may, however, cause long-term impairment. It has been reported that residual neuropsychological effects, as evidenced by greater cognitive impairments, persist even after abstinence (Pope and Yurgelun-Todd, 1996). Chan et al. (1998) have just presented ample evidence for Δ9-THC-induced neurotoxicity. Following treatment of cultured hippocampal neurons or slices with Δ9-THC, they observed shrinkage of neuronal cell bodies and nuclei as well as fragmentation of DNA, indicating neuronal apoptosis.

On the other hand, some effects of cannabinoids may be therapeutically useful, including antiemetic, analgesic, antispasmodic, appetite-stimulating and sleep-inducing effects (Childers and Breivogel, 1998). Antinociceptive effects of cannabinoids have been investigated in various animal models (e.g., Bridges et al., 2001; Calignano et al., 1998; Ibrahim et al., 2003; Malan et al., 2001, 2002; Martin et al., 1998; Pertwee, 1999; Rice et al., 2002; Richardson, 2000; Vaughan and Christie, 2000).

2. Endocannabinoid system

The endogenous cannabinoid system is comprised of cannabinoid receptors (CBrs), their endogenous ligands, i.e. endocannabinoids, and enzymes for their biosynthesis and degradation (Salzet, 2000). Endocannabinoids comprise a family of eicosanoid CBrs (Devane et al., 1992; Sugiura et al., 1995) present in the brain and in peripheral tissues. Ohno-Shosaku et al. (2001) and Wilson and Nicoll (2001) described that endogenous cannabinoids mediate retrograde signalling that may be involved in the inhibition of neurotransmitter release by cannabinoids.

The administration of endocannabinoids to experimental animals produces pharmacological and behavioural actions known to be associated with other cannabimimetic compounds. For instance, anandamide produces a characteristic tetrad of effects that includes antinociception, hypothermia, hypomobility, and catalepsy in mice after intravenous, intrathecal or intraperitoneal administration. The effects of anandamide occurred with a rapid onset, but with a rather short duration of action that is likely due to rapid uptake into neurons and astrocytes and subsequent enzymatic degradation (Calignano et al., 1998; Crawley et al., 1993; Fride and Mechoulam, 1993; Smith et al., 1994).

There are cannabinoid-dependent and cannabinoid-independent actions of endocannabinoids. CBr-related processes are involved in cognition, memory, anxiety, control of appetite, emesis, motor behaviour, sensory, autonomic and neuroendocrine responses. Endocannabinoids also induce hypotension and bradycardia, inhibit cell growth, affect energy metabolism and modulate immune responses. Moreover, along with their widely accepted anti-inflammatory effects, endocannabinoids can also exert pro-inflammatory actions, e.g., by enhancing eosinophil, neutrophil and natural killer cell migration (Alberich Jorda et al., 2004; Kishimoto et al., 2005; Oka et al., 2004, 2005).

The brain produces at least five compounds that possess submicromolar affinity for cannabinoid receptors: anandamide, 2-arachidonoylglycerol (2-AG), noladin ether, virodhamine, and *N*-arachidonoyldopamine (NADA). One common function of these and/or related compounds is to suppress pain sensitivity.

N-arachidonoylethanolamide (anandamide) is the first identified and best studied endocannabinoid (Devane et al., 1992). It binds to both CB1 and CB2 receptors (Glass and Northup, 1999), but its affinity for the CB2 receptor is approximately four-fold less than for CB1 receptors (Felder et al., 1995). The highest levels of anandamide were found in areas of the brain with the high densities of CBrs, such as the hippocampus, striatum, cerebellum and cortex (Egertova and Elphick, 2000). Anandamide is synthesised by postsynaptic neurons and acts as a retrograde messenger molecule to modulate neurotransmitter release from CB1-expressing presynaptic terminals (Egertova and Elphick, 2000).

In addition to CBrs, anandamide also activates the transient receptor potential vanilloid 1 receptor (TRPV1), behaving as a full agonist but with relatively low binding affinity (Zygmunt et al., 1999). The vasodilatory responses of isolated arteries exposed to anandamide were shown to be mediated through the TRPV1 receptor and to release calcitonin-gene-related peptide (CGRP) from perivascular sensory fibres (Ralevic et al., 2002; Zygmunt et al., 1999). Cellular co-expression of CB1 receptors and TRPV1 can result in enhancement of the biological effects induced by agonists of these receptors (Cristino et al., 2006). However, a recent study with fatty acid amide hydrolase (FAAH) and CB1 knockout mice indicates that CB1 receptor is the predominant target mediating anandamide's behavioural effects (Wise et al., 2007).

Anandamide is extremely unstable, and quickly hydrolysed by amidases (FAAH) yielding ethanolamine and arachidonic acid (Deutsch and Chin, 1993). The hydrolysis can be prevented by the use of amidase inhibitors like phenylmethylsulfonyl fluoride (PMSF) (Deutsch and Chin, 1993). Two mechanisms for anandamide inactivation have been identified in the brain (for review, see Di Marzo et al., 1999). The first is intracellular hydrolysis by FAAH. This membrane-associated enzyme is able to hydrolyse numerous fatty acid amides, including anandamide, 2-AG and oleamide. FAAH knockout mice possess 15-fold augmented levels of anandamide in their brains and display reduced pain sensation that was reversed by the CB1 antagonist SR141716A (rimonabant) (Cravatt et al., 2001).

A second major form of anandamide inactivation is presynaptic carrier-mediated uptake. Beltramo et al. (1997) have demonstrated the existence of a rapid, saturable transmembrane carrier. A high affinity transport system has a role in the breakdown of anandamide by removing this lipid mediator from the extracellular space and delivering it to intracellular metabolizing enzymes such as FAAH. Piomelli et al. (1999) originally described that anandamide transport

in neurons exhibits many of the same properties as do other neurotransmitter transport systems.

2-AG was the second endocannabinoid originally isolated from canine intestine (Mechoulam et al., 1995) and rat brain (Sugiura et al., 1995). 2-AG may be the natural ligand for both the CB1 and CB2 receptors (Suigiura and Waku, 2000). Although it exhibits a lower affinity for CB1 than anandamide, it is present in the brain at higher levels than anandamide. Therefore, 2-AG is considered the primary endogenous cannabinoid in the brain to be a full agonist at CB1 receptors (Childers and Breivogel, 1998). It was discovered that the synthesis or release of this lipid messenger requires both neuronal depolarization and external calcium (Childers and Breivogel, 1998). Biological activities of 2-AG have been reported in immune function, cell proliferation, embryo development, long-term potentiation in the hippocampus, neuroprotection and neuromodulation, cardiovascular function and inflammatory responses (for a review, see Suigiura and Waku, 2000).

The endocannabinoid 2-arachidonoyl glyceryl ether (noladin ether) has much higher affinity for CB1 than for CB2 receptors (Hanuš et al., 2001). The highest amount of this compound was detected in the thalamus and hippocampus and much lower amounts in the spinal cord (Fezza et al., 2002).

O-arachidonoylethanolamine (virodhamine) was identified in rat brain (Porter et al., 2002). Like anandamide, it appears to act as a partial agonist of CBrs (Walker et al., 2002).

N-arachidonoyldopamine (NADA) is another molecule with the arachidonic acid backbone that was found in rat and bovine brain (Huang et al., 2002). It activates CB1 receptors and elicits most of the cannabimimetic effects, including analgesia, after systemic administration. In addition, it activates TRPV1 receptors and causes hyperalgesia when administered peripherally (Huang et al., 2002). The distribution pattern of endogenous NADA in various brain areas differs from that of anandamide, with the highest levels found in the striatum and hippocampus. A small amount of NADA was also detected in the bovine DRG (Huang et al., 2002).

It is suggested that related endogenous fatty acid derivatives such as oleamide, palmitoylethanolamide, 2-lineoylglycerol, 2-palmitoylglycerol, and a family of arachidonoyl amino acids may interact with endocannabinoids to modulate pain sensitivity (Walker et al., 2002).

3. Cannabinoid receptors

The existence of CBrs was confirmed when Howlett showed that cannabinoids decreased cAMP in neuroblastoma cell cultures (Howlett, 1984), suggesting mediation by a $G_{i/o}$-coupled receptor (Howlett, 1985 Howlett and Fleming, 1984; Howlett et al., 1986). Determination and characterisation of a cannabinoid receptor from the brain was also obtained by immunohistochemical and radioligand binding methods (Devane et al., 1988). To date, at least two CBrs, the type 1 (CB1) and type 2 (CB2) receptors, have been described with regard to their primary structure, ligand-binding properties, and signal transduction systems (Howlett et al., 2002; Pertwee, 1995). CB1 and CB2 receptors belong to the large superfamily of receptors that couple to guanine-nucleotide-binding proteins and thread through cell membranes seven times (heptahelical receptors). CBrs contain an N-terminal extracellular domain that possesses glycosylation sites, a C-terminal intracellular domain coupled to a G protein complex, and 7 hydrophobic transmembrane segments connected by alternating extracellular and intracellular loops. Three-dimensional models of the helix bundle arrangement of human, rat and mouse CB1 and CB2 receptors have been constructed and compared (Bramblett et al., 1995; Onaivi et al., 1996).

The CBrs have been described in many species, including human, monkey, pig, dog, rat and mouse, but not insects. Initially, it was believed that the CB1 receptor was localised predominantly in the brain (central receptor for cannabinoids), whereas the CB2 receptor in peripheral cells and tissues derived from the immune system (peripheral receptor for cannabinoids) (reviewed by Ameri, 1999). However, the CB1 receptor has recently been found also in a number of peripheral tissues, such as the cardiovascular and reproductive systems as well as the gastrointestinal tract (Croci et al., 1998; Pertwee, 1997, 2001; Szabo et al., 2001; Wagner et al., 2001). On the other hand, the CB2 receptor was recently detected also in the central nervous system (CNS), e.g., in the microglial cells (Ashton et al., 2006; Kearn and Hilliard, 1997) as well as the neurons (Gong et al., 2006; Skaper et al., 1996).

The CB1 receptor cDNA was isolated first from a rat cerebral cortex library using an oligonucleotide probe derived from a member of G protein-coupled receptors (Matsuda et al., 1990). The gene locus for the human CB1 receptor has been localised in chromosome 6 to position 6q14–q15 (Caenazzo et al., 1991; Hoehe et al., 1991). The gene encoding the human CB2 receptor was cloned in 1993 and located in chromosome 1p36 (for a review, see Raitio et al., 2005). Human CB1 and CB2 receptors share 44% amino acid sequence identity throughout the total protein (Munro et al., 1993).

Both CB1 and CB2 receptors are coupled with G_i or G_o protein, negatively to adenylyl cyclase and positively to mitogen-activated protein (MAP) kinase. CB1 coupling to the G protein signal transduction pathways in presynaptic nerve terminals transduces the cannabinoid stimulation of MAP kinase and inhibition of adenylyl cyclase, thus attenuating the production of cAMP. CB1 are also coupled to ion channels through $G_{i/o}$ proteins, positively to A-type and inwardly rectifying potassium channels, and negatively to N-type and P/Q-type calcium channels and to D-type potassium channels (Howlett and Mukhopadhyay, 2000; Pertwee, 1997). Due to the decrease of cAMP accumulation, cAMP-dependent protein kinase (PKA) is inhibited by CB1 activation. In the absence of cannabinoids, PKA phosphorylates the potassium channel protein, thereby exerting decreased outward potassium current. In the presence of cannabinoids, however, the phosphorylation of the channel by PKA is reduced, which leads to an enhanced outward potassium current. Based on these findings, it has been suggested that cannabinoids play a role in regulating neurotransmitter releases. Inhibition of presynaptic calcium channels by cannabinoids likely reduces neurotransmitter release from CB1-expressing presynaptic terminals. It has been shown that cannabinoids are able to inhibit glutamate (Shen et al., 1996), acetylcholine (Gifford et al., 1997) and noradrenaline release (Schlicker et al., 1997). Presynaptic inhibition of neurotransmitter release by cannabinoids may turn out to be a key neuronal effect of cannabinoids.

The CB2 receptor is also coupled to $G_{i/o}$ proteins and thereby negatively coupled to adenylyl cyclase and the cAMP pathway in various types of cells (Howlett et al., 2002), and it stimulates mitogen-activated protein kinase (MAPK) cascades. Inwardly rectifying potassium channels can also serve as a signalling mechanism for the CB2 (Ho et al., 1999; McAllister et al., 1999). CB2 receptors are located principally in immune cells, among them leucocytes and those of the spleen and tonsils (Pertwee, 2001). One of the functions of CBrs in the immune system is modulation of cytokine release. Activation of B- and T-cell CB2 receptors by cannabinoids leads to inhibition of adenylyl cyclase in these cells and to a reduced response to immune challenge (Condie et al., 1996).

More recent evidence has shown that CB2 receptors are present in both cultured neuronal cells and the nervous systems of such mammals as rodents, monkeys and humans under normal conditions (see below). The CB2 receptor has been implicated in control of the proliferation, differentiation and survival of both neuronal and non-neuronal cells. This receptor might function as a "cell de-differentiation signal" by favouring a non-differentiated, proliferate state of cells (Fernández-Ruiz et al., 2007). In line with this notion, expression of the CB2 receptor is increased in glial (Sánchez et al., 2001) and breast (Caffarel et al., 2006) tumours. By contrast, studies conducted in glioma or astrocytoma cells (Sánchez et al., 2001) and in various non-neuronal cancer cells (Caffarel et al., 2006; Carracedo et al., 2006; Guzmán, 2003) showed that activation of the CB2 receptor induces apoptosis and inhibits tumour growth in host mice. These contrary

Table 1
Distribution of the CB1 receptors in the mammalian nervous system (PAG — periaqueductal gray; SN — substantia nigra; VTA — ventral tegmental area)

Intensity	Localisation	References
Dense	Telencephalon: – Layers II, III, IV of the somatosensory cortex, layer II of the cingulate cortex, layers II and IV of the entorhinal cortex, layer III of the piriform cortex, association cortical regions of the frontal lobe – Molecular layer of the dentate area, CA1, CA2 and CA3 fields of Ammon's horn, subicular complex – Ependymal and subependymal zones of the olfactory bulb, anterior olfactory nuclei, olfactory part of the anterior commissure – Amygdalar nuclei – Internal segment of the globus pallidus, caudate ncl. and putamen – Striatonigral pathway – Entopeduncular ncl. Brainstem: – SN pars reticulata – PAG – Gray matter around IV. Ventricle – Spinal trigeminal tract and ncl. Cerebellum: – Molecular layer Spinal cord: – Dorsal horn and lamina X DRG: – Medium and large-sized neurons	Farquhar-Smith et al. (2000), Glass et al. (1997), Herkenham et al. (1990, 1991a,b), Hohmann and Herkenham (1999a,b), Mailleux and Vanderhaeghen (1992), Tsou et al. (1997), Westlake et al. (1994)
Moderate	Telencephalon: – Layer V of the somatosensory cortex, temporal association cortex, secondary somatosensory and motor cortex, visual and auditory cortex – Polymorphic layer of the dentate area – Basal forebrain and septum – External segment of the globus pallidus, ventral pallidum, claustrum, and stria terminalis Diencephalon: – Anterior, mediodorsal, medioventral and intralaminar thalamic ncl. – Habenular ncl. – Lateral and paraventricular ncl. Of the hypothalamus, infundibular stem Brainstem: – Solitary tract ncl. – Ambiguus ncl. – Inferior olive Spinal cord: – Deep dorsal horn – Thoracic intermediolateral ncl.	Farquhar-Smith et al. (2000), Glass et al. (1997), Herkenham et al. (1990, 1991a,b), Mailleux and Vanderhaeghen (1992), Westlake et al. (1994), Tsou et al. (1997)
Low	Telencephalon: – Primary motor and somatosensory, visual and auditory cortex – Granule cell layer of the dentate gyrus – Olfactory tubercle – Ventral pallidum – Ncl. accumbens Diencephalon: – Sensory and motor thalamic ncll. – Subthalamic ncl. Brainstem: – Ventral tegmental area – SN pars compacta	Glass et al. (1997), Herkenham et al. (1990, 1991a,b), Mailleux and Vanderhaeghen (1992), Tsou et al. (1997), Westlake et al. (1994)

actions of the CB2 receptor would enable selective agonists of this receptor type to act by providing cytoprotection (Romero et al., 2002) or by eliciting apoptosis (Guzmán, 2003).

There is growing evidence that the CBrs play a key role in cannabinoid tolerance, induced predominantly as a consequence of pharmacodynamic events. Pharmacodynamic events like receptor down-regulation, receptor conformational change and receptor internalization are known to contribute to the development of tolerance (Ameri, 1999). The changes at receptor level cause a decrease in the interaction of ligand and receptor. A frequent phenomenon following exposure to drugs for a long period of time is receptor internalization. Internalization of receptor proteins means that receptors presented on the cell membrane are moved into the cytoplasm following binding of ligand to be either degraded or recycled. The internalization results in a decrease of receptor numbers at the cell surface and subsequently in a decrease of ligand-binding. On the other hand, the cells are able to reduce the amount of receptors themselves, plain down-regulation of the receptors. Indeed, development of tolerance to Δ9-THC, which is accompanied by down-regulation of CBrs, has been observed. This can serve as one of possible mechanisms developing tolerance to cannabinoids the magnitude of which is not uniform throughout the brain (Martin et al., 2004; Martin, 2005). Populations of CB1 receptors in some brain regions are to down-regulation more resistant what is prolonging the onset of tolerance regulation, thus, specific tolerance to cannabinoid effects occurs effecting specific site of action (Breivogel et al., 1999). The tolerance to Δ9-THC, which is accompanied by down-regulation of CBrs, has been observed in the striatum, cerebellum and limbic forebrain, but not in the ventral mesencephalon (Oviedo et al., 1993; Rodriguez de Fonseca et al., 1994). Although CB1 receptor binding decreases after chronic Δ9-THC exposure in most of the brain's regions, this is not accompanied by simultaneous decrease of CB1 receptor mRNA levels (Romero et al., 1997). This indicates that the primary action of Δ9-THC would be on the receptor protein itself rather than on the expression of the CB1 receptor gene (Ameri, 1999). The mechanisms of CB1 receptor down-regulation (synthesis, degradation, internalization) are far from being completely understood yet (González et al., 2005).

There was also described an inverse tolerance, so called behavioural sensitization to cannabinoid agonist effects after repeated administration (Cadoni et al., 2001). Sensitization refers to the augmentation of at least some of behavioural responses to many drugs of abuse that occurs during their repeated administration and persists long after drug exposure is discontinued (Robinson and Berridge, 1993). These findings with cannabinoids could be explained besides other possible mechanisms by up-regulation of CB receptors (Landa and Jurajda, 2007; Rubino et al., 2003).

There is a growing body of evidence that some cannabinoid effects are not mediated by either CB1 or CB2 receptors, therefore suggesting the presence of additional receptors. The existence of multiple cannabinoid receptors and their functions, specifically the cloned CB1 and CB2 receptors, and at least 3 non-CB1/CB2 cannabinoid receptors, is under consideration (Mackie and Stella, 2006). The evidence for other CB-like receptors is based on bioassays with compounds lacking significant affinity for CB1 or CB2 receptors but that are sensitive to CB1- or CB2-selective antagonists (Calignano et al., 1998, 2001). Other studies described residual activities of (endo) cannabinoids in CB1 or CB2 knockout mice (see e.g. Baskfield et al., 2004; Di Marzo et al., 2000; Griffin et al., 1997). For example, some of the effects of such endocannabinoids as anandamide are mediated by TRPV1 (Zygmunt et al., 1999). Additional receptor targets for cannabinoids include the orphan G-protein-coupled receptor GPR55 (Baker et al., 2006), the endothelial cannabinoid receptor or hippocampal non-CB1 receptor (Begg et al., 2005).

4. Distribution of cannabinoid receptors in the nervous system structures

4.1. CB1 receptors

The regional distribution of CB1 receptors has been characterised in rat and human brains as corresponding with the behavioural effects of cannabinoids (Glass et al., 1997; Herkenham et al., 1990, 1991a,b; Mailleux and Vanderhaeghen, 1992; Tsou et al., 1997; Westlake et al., 1994). The CB1 receptor expression was detected in regions influencing a number of key functions, including mood, motor coordination, autonomic function, memory, sensation and cognition. Electron microscopy studies demonstrated CB1 receptors predominantly on presynaptic terminals (Katona et al., 1999; Marsicano and Lutz, 1999; Tsou et al., 1999), but they were found also on postsynaptic structures and glia (Rodríguez et al., 2001). Generally, a decline of CB1 receptor genes expression in human and rodent brains during aging is suggested (Westlake et al., 1994).

A review of the nervous system structures displaying CB1 receptors is summarised in Table 1. A high density of CB1 receptors was found in the hippocampus, some olfactory regions, caudate, putamen, accumbens nucleus (ventral striatum), the substantia nigra pars reticulata (SNr), globus pallidus, and the horizontal limb of the diagonal band. A presence of CB1 receptors in the hippocampus in high density is related to frequently described disruptive effects of cannabinoids on memory and cognition (Herkenham et al., 1990, 1991b). Chronic exposure to Δ9-THC or marijuana extracts persistently alters the structure and function of the hippocampus (Scallet, 1991), which is involved in learning and memory processes in both rats and humans.

The occurrence of CB1 receptors in the basal ganglia and the effects of cannabinoids in these structures imply that endogenous cannabinoids may play an essential role in the fine-tuning of motor control. Indeed, several reports have demonstrated disturbances in CB1 receptor expression and binding in neurological disorders of the extrapyramidal system. Thus, CB1 binding is decreased in neurodegenerative diseases, such as Parkinson's and Huntington's (Glass et al., 1993; Richfield and Herkenham, 1994; Sañudo-Peña et al., 1998).

There is a high density of CB1 receptors in the rat cerebellum (Matsuda et al., 1993), which may have a role in the ataxia, immobility, and catalepsy observed following acute administration of Δ9-THC and other cannabinoids in various experiments (Fonseca et al., 1998). In contrast, a relatively low density of CB1 receptors found in the human cerebellum is consistent with the more subtle defects noted in human gross motor functioning after marijuana use (Ameri, 1999; Herkenham et al., 1990).

Some regions of the brain display a moderate density (neocortex, basal amygdala, medial hypothalamus, solitary nucleus), while others like the thalamus and brain stem exhibit low levels of CB1 receptors.

The CB1 receptors, among other things, play an important role in the central and peripheral regulation of food intake, fat accumulation, and lipid and glucose metabolism. Alterations of these functions are associated with cannabinoid CB1 receptor system hyperactivity (Gelfand and Cannon, 2006) in both CNS and peripheral tissues (adipocytes, skeletal muscle cells, liver, gastrointestinal tract). Stimulation of the hypothalamic CB1 receptors interacts with neuropeptides regulating energetic homeostasis, food intake and lipogenesis in visceral tissues (Cota et al., 2003). The activity of the central CB1 receptors rises also with increasing levels of leptin released from adipose tissues (Pagotto and Pasquali, 2005). Stimulation of central CB1 receptors in the accumbens nucleus invigorates the dopaminergic reward pathway and thus the motivation to eat, as well as to smoke or intake drugs of abuse. CB1 receptors located in the ventral tegmental area (VTA) on presynaptic glutamatergic and GABAergic neurons act as retrograde inhibiting modulators influencing their input to VTA dopaminergic neurons which is believed to activate the reward pathway (Maldonado et al., 2006). Microinjections of Δ9-THC into the posterior VTA and into the posterior shell of nucleus accumbens produced reinforcing effects of such drugs as amphetamines, cocaine, heroin, and nicotine which are all thought to have there their sites of rewarding action (Zangen et al., 2006).

CB1 receptors are highly expressed in the areas that are involved in pain modulation, including the periaqueductal gray (PAG; Tsou et al., 1997) and the dorsal horn of the spinal cord (Farquhar-Smith et al., 2000). CB1 receptors have also been detected in dorsal root ganglia (DRG) neurons of different sizes with variable degrees of CB1 mRNA and protein localisation (Ahluwalia et al., 2000; Bridges et al., 2003; Hohmann and Herkenham, 1999b; Price et al., 2003; Salio et al., 2002). The co-expression of CB1 receptors with various markers of neuronal subpopulations demonstrated that CB1 receptors are present in the majority (76–83%) of nociceptive neurons of the DRG (Ahluwalia et al., 2000; Mitrirattanakul et al., 2006). CB1 receptors are synthesised in the bodies of DRG neurons and transported to their central and peripheral axonal branches (Hohmann and Herkenham, 1999a,b).

4.2. CB2 receptors

CB2 receptors are widely distributed in peripheral tissues, and particularly in immune tissues. Expression of the CB2 receptor gene transcripts were found in the spleen, tonsils, thymus, mast cells and blood cells (Berdyshev, 2000; Munro et al., 1993; Suigiura and Waku, 2000; Wilson and Nicoll, 2001). While CB2 receptors have not been found in the intact CNS by some authors (Carlisle et al., 2002; Chakrabarti et al., 1995; Derocq et al., 1995; Galiegue et al., 1995; Griffin et al., 1999; Shatz et al., 1997; Sugiura et al., 2000), others have demonstrated CB2 expression in rat microglial (Kearn and Hilliard, 1997) and cerebellar granule cells (Skaper et al., 1996), as well as in adult rat retina (Lu et al., 2000). In contrast to previously described predominant presynaptic localisation of CB1 receptors in the brain, immunoreactivity suggests postsynaptic localisation of CB2 receptors is more likely (Gong et al., 2006; Onaivi et al., 2006). Recent studies have detected multifocal expression of CB2 immunoreactivity in rat and murine brains at levels much lower than those of CB1 receptors (Gong et al., 2006; Onaivi et al., 2006).

Table 2
Distribution of CB2 receptors in the mammalian nervous system (PAG — periaqueductal gray; SN — substantia nigra; VTA — ventral tegmental area)

Intensity	Localisation	References
Dense	Telencephalon: – Neurons of the layers III and V of the orbital, visual, auditory, motor and piriform cortex – Island of Calleja – Pyramidal neurons of the hippocampal CA2 and CA3 – Anterior olfactory ncl. – Striatum, amygdalar ncll. Diencephalon: – Ventral and lateral posterior, posterior, and paracentral thalamic ncll. – Retina Brainstem: – Dorsal cochlear ncl. – Facial ncl. Cerebellum: – Purkinje cell bodies – Cerebellar granule cells DRG: – Neurons of a neonatal rat	Gong et al. (2006), Lu et al. (2000), Onaivi et al. (2006), Ross et al. (2001), Skaper et al. (1996)
Moderate	Diencephalon: – Geniculate body ncll. Brainstem: – SN pars reticulata — neurons larger than 20 μm – PAG – Inferior colliculus, interpeduncular, paratrochlear, and red ncll. – Paralemniscal ncl., dorsal ncl. of lateral lemniscus – Pontine ncll. – Paratrochlear ncl, medial and lateral vestibular ncll. – Parvocellular reticular ncl. – The spinal trigeminal tract ncl. Cerebellum: – Dendrites of Purkinje cells in the molecular layer	Gong et al. (2006), Onaivi et al. (2006)
Low	Diencephalon: – Paraventricular and mediodorsal thalamic ncll. – Ventromedial and arcuate hypothalamic ncll.	Gong et al. (2006)

A review of the nervous system structures displaying CB2 receptors is summarised in Table 2. The most prominent staining for CB2 receptor was observed in the anterior olfactory nucleus, in the neurons of the piriform, orbital, visual, motor and auditory cortex, where bodies and apical dendrites of pyramidal neurons in the layers III and V were heavily stained. In addition, pyramidal neurons of the hippocampal allocortex, particularly in CA2 and CA3 and some glial cells, also displayed from moderate to dense CB2 immunostaining. Some thalamic nuclei exhibited prominent cell bodies with CB2 immunostaining, while reticular thalamic nucleus contained a dense plexus of CB2 immunoreactive fibres.

Moderate density of CB2 immunopositive cell bodies were found in the periaqueductal gray (PAG), substantia nigra pars reticulata, and other nuclear structures of the brain stem (see Table 2). Purkinje cell bodies over all of the cerebellar lobules were intensely immunostained and their dendrites in the molecular layer moderately so.

CB2 receptor mRNA was not detected by in situ hybridization in the intact DRG (Hohmann and Herkenham, 1999b) or trigeminal ganglia (Price et al., 2003), but the DRG neurons from neonatal rats cultivated in vitro displayed CB2 receptors (Ross et al., 2001). Recently, CB2 immunoreactivity was described in the large dermal myelinated nerve fibres, small subepidermal fascicles of unmyelinated fibres and single epidermal nerve fibres of normal human skin (Ständer et al., 2005).

5. Therapeutic potential of cannabinoids

Endocannabinoids are released after a triggering signal, when it is necessary to maintain homeostasis. These findings opened the way for research into the physiological and pathophysiological roles of the endocannabinoid system, with a subsequent goal of searching for new compounds that could modulate, when administered exogenously, its regulatory abilities and serve as pharmacotherapeutical agents. De novo sythesized substances with an affinity to cannabinoid receptors act either as agonists simulating the activity of endocannabinoids, or as antagonists preventing the binding of endocannabinoids and thus inhibiting the activity of the endocannabinoid system. Cannabinoid receptor agonists as well as agents that might modify cannabinoid transport or metabolism and that way increase the endocannabinoid system activity are likely to be used as potential hypnotics, analgesics, antiemetics, antiasthmatics, antihypertensives, immunomodulatory drugs, anti-inflammatory and neuroprotective agents, antiepileptics, drugs for treatment of glaucoma, spasticity and other "movement disorders", eating disorders, or alcohol withdrawal (Grant and Cahn, 2005; Grotenhermen and Russo, 2002; Mackie, 2006; Martin, 2002; Pertwee, 2000; Porter and Felder, 2001; Rondon, 2001; Williamson and Evans, 2000). CB2 receptor modulation has been implicated in processes as diverse as analgesia, hepatic fibrosis, bone growth, and atherosclerosis (Mackie and Ross, 2008). One of the CB1 receptor antagonists, rimonabant, was authorized after the completion of a 2-year clinical trial (Sanofi–Aventis) for use in human medicine as a drug reducing the development of cardiometabolic risk factors (Pagotto et al., 2007).

6. Cannabinoid receptor ligands

Cannabinoid receptor agonists and antagonists were reviewed in several studies (e.g., Barth and Rinaldi-Carmona, 1999; Di Marzo et al., 1999; Howlett et al., 2002; Martin et al., 1999; Mechoulam et al., 1998; Pertwee, 1999; Schlicker and Kathmann, 2001).

6.1. Agonists

Progress in identifying CBrs came from the development of potent agonists, which can be subdivided into four groups according to their

chemical structures (Childers and Breivogel, 1998). The first group (classical cannabinoids) involves dibenzopyran derivatives that are both natural constituents of cannabis (e.g., Δ9-THC and Δ8-THC) and their synthetic analogues (HU 210). The first generation of classical cannabinoids lacked CB1/CB2 selectivity but they were developed by making relatively minor changes to the THC molecule (CB2-selective agonists; e.g., JWH-133 and HU-308) (Gareau et al., 1996; Hanuš et al., 1999; Huffman et al., 1996). The second group (non-classical cannabinoids) was developed as bicylic and tricyclic analogues of Δ9-THC lacking the pyran ring (Johnson and Melvin, 1986; Melvin et al., 1993). This group includes the main cannabinoid agonist, CP55940, which binds to both CB1 and CB2 receptors with similar affinity and displays high activity in vivo. It is 10 to 50 times more potent than Δ9-THC in the mouse model (Johnson and Melvin, 1986). CP55940 behaves as a full agonist for both receptor types. The third group of cannabimimetic compounds contains the aminoalkylindoles. This series is represented by WIN 55212-2, which displays high affinity for both CBrs, albeit with moderate selectivity in favour of the CB2 receptors. Some of these aminoalkylindoles have been found to display significant selectivity for the CB2 (e.g. JWH-015; Gallant et al., 1996; Showalter et al., 1996). The prototype of the fourth eicosanoid group, which involves arachidonic acid derivatives, is anandamide, the first endogenous cannabinoid isolated from mammalian brain (Devane et al., 1992).

Behavioural effects of cannabinoid agents in animal models have been reviewed by Chaperon and Thiébot (1999). Cannabinoid agonists such as WIN55-212-2 and CP55-940 produce a characteristic combination of four prototypic profiles (response to the tetrad tests) including catalepsy, analgesia, hypoactivity and hypothermia (Pertwee and Ross, 1991). These effects are reversed by the selective CB1 antagonist SR141716A (rimonabant), providing evidence for the involvement of CB1-related mechanisms (Rinaldi-Carmona et al., 1994). Although, many cannabinoid receptor ligands show only little or modest selectivity for both CBrs, a number of synthetic compounds are known to have significant selectivity for the CB2 receptors (Huffman, 2005). CB2-selective agonists lack psychoactivity effect and so CB2 receptors are considered to be interesting targets for treating neurological disorders (Fernández-Ruiz et al., 2007).

Some effects of cannabinoid receptor agonists show a biphasic behaviour that is dependent upon dose. For example, low doses of anandamide stimulated leukocyte phagocytosis and aggressive behavioural activities while high doses caused inhibitory effects on this immune function and decreased aggressiveness in mice (Sulcova et al., 1998).

One of most well-characterised biological effects of cannabinoids is their capability to inhibit pain transmission. Cannabinoids are effective as analgesics in acute (phasic) pain as well as chronic (tonic) pain (for a review, see Pertwee, 2001). Cannabinoids modulate nociceptive processing through central (Hohmann et al., 1995, 1999; Martin et al., 1996; Richardson et al., 1998a; Tsou et al., 1996) and peripheral (Calignano et al., 1998; Jaggar et al., 1998; Richardson et al., 1998b) mechanisms. The majority of these effects are mediated by CB1 receptors located in both the central and peripheral nervous systems. Although CB2 receptors were detected in the nervous system in much lower levels than CB1 receptors (Gong et al., 2006; Onaivi et al., 2006), CB2-selective ligands are more effective in animal models of hyperalgesia (Hanuš et al., 1999; Hohmann et al., 2004; Malan et al., 2001; Nackley et al., 2004). A number of studies reported on the relationship between dose of cannabinoid and a degree of antinociception (for a review, see Pertwee, 2001).

The analgesic effect of cannabinoids is attributed in particular to CBrs located in structures that mediate nociceptive neurotransmission, including the dorsal horn of the spinal cord and the PAG (Herkenham et al., 1991b), the dorsal raphe nuclei (Martin et al., 1995), and the thalamic ventroposterolateral nucleus (Martin et al., 1996). The PAG is involved in ascending pain transmission, since it receives afferents from nociceptive neurons of the spinal cord and sends projections to thalamic nuclei. As shown by Lichtman and Martin (1991), the antinociception induced by systemically administered cannabimimetic compounds is significantly attenuated by spinal transection. This indicates that the mechanisms of action for the cannabinoid-induced analgesia include both spinal and supraspinal actions. The PAG is also a major component of a descending pain inhibitory system. Activation of this system inhibits nociceptive neurons in the dorsal horn of the spinal cord (Behbehani, 1995).

However, some studies report on the existence of signalling differences between CBrs of the brain and spinal cord involved in cannabinoid-induced antinociception (Welch et al., 1995, 1998). The cannabinoid receptor system also participates in the descending noradrenergic control of nociception mediated by the neurotransmitters noradrenaline and serotonin (Lichtman and Martin, 1991). Inhibition of the descending system slows the mean discharge rates of the nociceptive neurons in the dorsal horn of the spinal cord. Electrophysiological experiments provide evidence that CBrs in the primary sensory neurons of the DRG are also involved in the antinociception. The antihyperalgesic efficacy of locally administered CB1 agonist was increased because up-regulation of CB1 receptors is induced by peripheral inflammation (Amaya et al., 2006) or neuropathy (Mitrirattanakul et al., 2006). This indicate the possibility to develop novel therapeutics that target the peripheral endocannabinoid system and provide pain relief without the side effects associated with central CB1 receptor activation (Mitrirattanakul et al., 2006). There is no doubt that cannabinoids induce antinociception in animal models of both acute and chronic pain through activating CB1 receptors. However, not all types of antinociception induced by cannabinoids seem to be mediated by the same cannabinoid receptor subtypes (for a review, see Pertwee, 1999). On the other hand, the antinociception may be mediated by CB2 or CB2-like receptors, as was shown in experiments with CB2 receptor-selective agonists and antagonists (Calignano et al., 1998; Hanuš et al., 1999). This shows promise for the treatment of acute and chronic pain, because CB2 receptor activation inhibits pain responses without the adverse and most often psychotropic effects produced by CB1 agonists (Malan et al., 2002).

Another important physiological role of endocannabinoids is neuroprotection (Mechoulam and Shohami, 2002). Ischemia and hypoxia in the CNS induce abnormal glutamate hyperactivity and other processes that cause neuronal damage. These processes play a role in chronic neurodegenerative diseases such as Parkinson's and Alzheimer's, as well as multiple sclerosis. The levels of endocannabinoids increase following a neurotoxic insult. Neuroprotective effects of cannabinoid mechanisms observed in animal studies include inhibition of excessive glutamate production, inhibition of calcium influx into cells, antioxidant properties reducing damage caused by oxygen radicals, and modulation of vascular tone (Grundy, 2002; Hampson, 2002; Mechoulam and Shohami, 2002). Modulation of cannabinoid receptor tone affects the outcome following neurotoxic insult. The resultant response appears to be dependent upon a number of factors, since in some cases the cannabinoid receptor agonists show neuroprotective effects (see e.g., Martínez-Orgado et al., 2003; Mauler et al., 2002; Nagayama et al., 1999; Panikashvili et al., 2001; van der Stelt et al., 2001) while in other studies it is rimonabant that is neuroprotective (Berger et al., 2004; Hansen et al., 2002). Another important aspect of neuroprotection is the involvement of neuroinflammation (Fowler et al., 2005). The notion that cannabinoids may be useful in countering neuroinflammation has been particularly well studied in animal experimental models of multiple sclerosis (for reviews, see Baker et al., 2003; Walter and Stella, 2004). The role of cannabinoids in neuroprotection has been reviewed in detail elsewhere (Fowler, 2003).

6.2. Antagonists

The first specific cannabinoid antagonist was SR141716A (rimonabant) (Rinaldi-Carmona et al., 1994). It blocks the actions of various

cannabinoid agonists in vivo (Compton et al., 1996). This compound is a pure antagonist at low (nanomolar) concentrations, with higher potency and selectivity for CB1 than CB2 receptors. Although SR141716A is CB1-selective, it is not CB1-specific and it blocks both CB1 and CB2 receptors at sufficiently high doses (Pertwee, 1999). Whereas in many experiments on cannabinoid-induced antinociception low doses of SR141716A attenuated the degree of antinociception, CB2-selective antagonist, SR144528, did not (Calignano et al., 1998).

When administered by themselves, the aforementioned antagonists at the cannabinoid receptor may behave as inverse agonists in several bioassay systems. This means that they not only block the effects of endocannabinoids but produce effects that are opposite in direction from those produced by cannabinoid receptor agonists — e.g. causing hyperalgesia (Jaggar et al., 1998) — and suggesting that the cannabinoid system is tonically active. This tonic activity may be due to a constant release of endocannabinoids or results from a portion of cannabinoid receptors existing in a constitutively active state (Pertwee, 2001). Tonic activity of the cannabinoid system has been demonstrated in several conditions. Elevated levels of endocannabinoids have been demonstrated in a pain circuit of the brain (periaqueductal gray) following painful stimuli (Walker et al., 1999). Tonic control of spasticity by the endocannabinoid system has been observed in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice, an animal model of multiple sclerosis (Baker et al., 2001). An increase of cannabinoid receptors following nerve damage was demonstrated in a rat model of chronic neuropathic pain (Siegling et al., 2001).

Two analogues of SR141716A that have also been used to block CB1 receptor-mediated effects are AM251 and AM281 (Howlett et al., 2002). On the other hand, AM630 is a CB2-selective antagonist/inverse agonist. It has been shown to potently reverse CP55940-induced inhibition, and when administered by itself enhancement of forskolin-stimulated cyclic AMP production (Ross et al., 1999).

Cannabinoid CB1 antagonists are promising new medications for drug dependence (Le Foll and Goldberg, 2005). The cannabinoid receptor antagonist AM251 inhibited the intake of methamphetamine in rats trained to i.v. self-administration of this drug (Vinklerova et al., 2002), and pre-treatment combining methamphetamine and AM251 suppressed in rats the development of sensitization to both psychostimulant and anti-aggressive effects (Landa et al., 2006). Cannabinoid receptor CB1 knockout mice did not show a tendency to develop nicotine dependence in models of the conditioned place preference and the drug-self-administration (Forget et al., 2005). The same effects were seen in their wild-type littermates by administration of the selective CB1 receptor antagonist rimonabant (SR141716A).

7. Conclusion

There is clear evidence that the recently discovered endocannabinoid system, with its specific receptors and their ligands, is involved in regulating a number of physiological functions. At present, many intensive studies aim to reveal how the behavioural actions can be dissociated from the therapeutic properties of marijuana and cannabinoids. An increasing number of synthetic compounds that act as selective ligands of specific cannabinoid receptors with either agonistic or antagonistic efficacy are available. These, along with other approaches for exogenously influencing the activity of the endocannabinoid system, can contribute to the progress in developing new therapeutic drugs with less of the adverse effects described after intake of marijuana, which contains a mixture of about 60 cannabinoids (Di Marzo and Petrosino, 2007).

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