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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

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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).

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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