

# Cannabinoid Receptors

## Key References

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## Overview

Cannabinoid receptors derive their name from  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), the psychoactive principle in *Cannabis sativa* (marijuana). Although marijuana has been in use for over 4,000 years as a therapeutic agent and as a recreational drug, it was not until the 1980s that evidence revealed a receptor based mechanism of action.  $\Delta^9$ -THC was shown to modulate cAMP formation, and a binding site for the high affinity cannabinoid agonist, CP-55,940, was identified in mammalian brain.

In 1992, the first cannabinoid receptor, CB<sub>1</sub>, was cloned and classified as a member of the family of G protein-coupled receptors. The CB<sub>1</sub> cannabinoid receptor is found in high abundance in brain neurons, with highest levels expressed in basal ganglia, cerebellum, hippocampus and cerebral cortex. Considerably lower expression is found in peripheral tissue including lung, testis, uterus, and vascular tissue. Following agonist binding, CB<sub>1</sub> receptors couple to the inhibition of adenylyl cyclase, inhibition of N- and Q-type voltage-operated calcium channels, and stimulation of inwardly rectifying and A type potassium channels.

A second cannabinoid receptor, CB<sub>2</sub>, was cloned in 1993 with 44% identity at the amino acid level to the CB<sub>1</sub> receptor. The CB<sub>2</sub> receptor is found in cells of the peripheral immune system and is coupled to inhibition of adenylyl cyclase, but does not appear to couple to ion channel regulation. A third and apparently rare human cannabinoid receptor, CB<sub>1A</sub>, is an alternatively spliced form of the human CB<sub>1</sub> receptor characterized by a loss of 28 amino acids from the N terminus. This shorter mRNA may be poorly transcribed in

humans and does not appear to be expressed in rat or mouse. It should be noted that IUPHAR nomenclature, if applied to these receptors, might result in the renaming of the CB<sub>1</sub> receptor to CB<sub>1a</sub> and the splice variant would then become CB<sub>1b</sub>.

Many cannabinoid receptor agonists have been synthesized and extensively studied including analogs of the tricyclic benzopyran  $\Delta^9$ -THC, such as HU 210, the bicyclic analogs typified by CP-55,940, and the amino-alkylindoles such as WIN 55212-2. Few selective ligands are available for the CB<sub>1</sub> and CB<sub>2</sub> receptors. Both receptors have essentially equal affinity for many cannabinoid agonists including  $\Delta^9$ -THC, CP-55,940, HU 210, levonantradol and nabilone. Recently, selective antagonists have been synthesized for both the CB<sub>1</sub> (SR 141716A, LY-320135, AM251) and CB<sub>2</sub> (SR144528) receptors. Agonists with moderate selectivity include WIN 55212-2, JWH-015, and JWH-133 which exhibit between 30 and 70 fold selectivity for CB<sub>2</sub> over CB<sub>1</sub> receptors.

Analogous to the discovery of the endogenous opiate receptor agonists, enkephalin and endorphin, the presence of cannabinoid receptors suggested that endogenous cannabinoids might be present in mammalian brain. The lipid anandamide (arachidonyl-ethanolamide) and subsequently 2-arachidonyl glycerol were isolated from mammalian tissue and were shown to be functional cannabinoid receptor agonists. The storage, release, metabolism and physiological role of these and possibly other lipid neurotransmitters are currently under intense investigation. Recent studies have shown that the transient suppression of GABA-mediated

transmission following depolarization of hippocampal pyramidal neurons is mediated by retrograde signaling through the release of endogenous cannabinoids. Signaling by the endocannabinoid system may thus represent a mechanism by which neurons can communicate backwards across synapses in order to modulate their inputs.

Cannabinoids have been shown to possess therapeutic potential in the treatment of emesis, cachexia, pain, muscle spasms and other conditions, but psychotropic side effects preclude their widespread use. Development of high affinity and selective cannabinoid receptor ligands or modulation of endo-cannabinoid concentrations *in vivo* may improve the therapeutic potential of modulating the cannabinoid receptor system.

# Cannabinoid Receptors

CURRENTLY ACCEPTED NAME	CB <sub>1</sub>	CB <sub>2</sub> (C-243)
STRUCTURAL INFORMATION	472 aa (human)	360 aa (human)
LOCATION	Brain Less abundant in periphery	Peripheral immune cells
ENDOGENOUS AGONISTS	Anandamide (A 0580) 2-Arachidonyl glycerol (A-261)	Anandamide (A 0580) 2-Arachidonyl glycerol (A-261)
RECEPTOR SELECTIVE AGONISTS	Δ <sup>9</sup> -THC (T 2386) CP-55,940 (C 1112) R(+)-WIN 55,212-2 (W-102) HU 210 (H 7909) Levonantradol Nabilone Methanandamide (M-186)	Δ <sup>9</sup> -THC (T 2386) CP-55,940 (C 1112) R(+)-WIN 55,212-2 (W-102) HU 210 (H 7909) Levonantradol Nabilone Methanandamide (M-186) JWH-015 (J 4252) JWH-133 (J 2753)
RECEPTOR SELECTIVE ANTAGONISTS	SR 141716A LY-320135 AM251	SR 144528
SIGNAL TRANSDUCTION MECHANISMS	G <sub>i</sub> (cAMP modulation) Decrease voltage-sensitive Ca <sup>2+</sup> channels (N-, Q-type) Increase K <sub>ir</sub> and K <sup>+</sup> A conductance	G <sub>i</sub> (cAMP modulation)
RADIOLIGANDS OF CHOICE	[ <sup>3</sup> H]-CP-55,940 [ <sup>3</sup> H]-WIN 55,212-2 [ <sup>3</sup> H]-SR 141716A [ <sup>3</sup> H]-HU 243	[ <sup>3</sup> H]-CP-55,940 [ <sup>3</sup> H]-WIN 55,212-2 [ <sup>3</sup> H]-HU 243

## ABBREVIATIONS

**AM251:** N-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide  
**CP-55,940:** (-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)-phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol  
**HU 210:** (-)-11-Hydroxy-Δ<sup>8</sup>-tetrahydrocannabinol-dimethylheptyl  
**HU 243:** (6aR,9R,10aR)-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol  
**JWH-015:** (2-Methyl-1-propyl-1H-indol-3-yl)-1-naphthalenyl-methanone  
**JWH-133:** (3-(1'1'Dimethylbutyl)-1-deoxy-Δ<sup>8</sup>-tetrahydrocannabinol  
**LY-320135:** 4-[6-Methoxy-2-(4-methoxy-phenyl)-benzofuran-3-carbonyl]-benzoxazole  
**SR 141716A:** N-Piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide  
**SR 144528:** N-[(1S)-endo-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-pyrazole-3-carboxamide  
**Δ<sup>9</sup>-THC:** Δ<sup>9</sup>-Tetrahydrocannabinol  
**WIN 55,212-2:** [2,3-Dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-yl)-(1-naphthalenyl)methanone