

Cannabinoid Receptors

Key References

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Overview

Cannabinoid receptors derive their name from Δ^9 -tetrahydrocannabinol (Δ^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. Δ^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 1990, the first cannabinoid receptor, CB₁, was cloned and classified as a member of the family of G protein-coupled receptors. The CB₁ 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, CB₁ 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, CB₂, was cloned in 1993 with 44% identity at the amino acid level to the CB₁ receptor. The CB₂ receptor is found primarily in cells of the peripheral immune system with sparse expression in neurons and immune cells of the CNS. The CB₂ receptor 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_{1A}, is an alternatively spliced form of the human CB₁ 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 CB₁ receptor to CB_{1a} and the splice variant would then become CB_{1b}. Pharmacological evidence suggests additional cannabinoid-like receptors exist that have yet to be identified at the molecular level.

Many cannabinoid receptor agonists have been synthesized and extensively studied, including analogs of the tricyclic benzopyran Δ^9 -THC, such as HU 210, the bicyclic analogs typified by CP-55,940, and the amino-alkylindoles such as WIN 55212-2. Both receptors have essentially equal affinity for many cannabinoid agonists including Δ^9 -THC, CP-55,940, HU 210, WIN 55212-2, levonantradol and nabilone. Recently, selective agonists and antagonists have been synthesized for both the CB₁ and CB₂ receptors (see table) providing useful pharmacological tools that compliment the available CB₁, CB₂ and CB₁/CB₂ knockout mice.

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 N-arachidonoyl-ethanolamide (anandamide) and subsequently 2-arachidonoyl-glycerol (2-AG), 2-arachidonoyl-glycerol ether (2-AGE), N-arachidonoyl-dopamine (NADA), and O-arachidonoyl-ethanolamine (virhodamine) were isolated from mammalian tissue and were shown to be functional cannabinoid receptor agonists. Anandamide fulfills all the requirements to be classified as a neurotransmitter except that it appears to be stored as a phospholipid precursor that is released by calcium-dependent

phospholipase D enzymatic cleavage. An energy- and ion-independent transport of anandamide into neurons has been characterized, but not identified at the molecular level. Intracellular fatty acid amidohydrolase (FAAH) splits anandamide into arachidonic acid and ethanolamine that provides the chemical gradient to allow the specific transport of anandamide across the plasma membrane. 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. Similar retrograde signaling has been observed in modulation of dopamine and glutamate release. Signaling by the endocannabinoid system may thus represent a feedback mechanism by which postsynaptic neurons can modulate presynaptic output.

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 orthosteric or allosteric cannabinoid receptor ligands, restricting CNS penetration, or modulation of endocannabinoid concentrations by targeting the transporter, phospholipase D or FAAH proteins, may improve the therapeutic potential of modulating the cannabinoid receptor system.

Cannabinoid Receptors

CURRENTLY ACCEPTED NAME	CB ₁	CB ₂ (C243)
STRUCTURAL INFORMATION	472 aa (human)	360 aa (human)
ENDOGENOUS AGONISTS	N-Arachidonylethanolamine (A0580), 2-Arachidonoyl-glycerol (A261), 2-Arachidonoyl-glycerylether, N-Arachidonoyl-dopamine, O-Arachidonoyl-ethanolamine	N-Arachidonylethanolamine (A0580), 2-Arachidonoyl-glycerol (A261), 2-Arachidonoyl-glycerylether, N-Arachidonoyl-dopamine (A8848), O-Arachidonoyl-ethanolamine (V2389)
RECEPTOR SELECTIVE AGONISTS	Δ ⁹ -THC (T2386), CP-55,940 (C1112), R(+)-WIN 55,212-2 (W102), HU 210 (H7909), Levonantradol, Nabilone (N3785), Methanandamide (M186), ACEA (A9719), O-1812	Δ ⁹ -THC (T2386), CP-55,940 (C1112), R(+)-WIN 55,212-2 (W102), HU 210 (H7909), Levonantradol, Nabilone (N3785), Methanandamide (M186), JWH-015 (J4252), JWH-133 (J2753)
RECEPTOR SELECTIVE ANTAGONISTS	SR 141716A, LY-320135, AM251 (A6226), AM281 (A0980)	SR 144528, AM630
SIGNAL TRANSDUCTION MECHANISMS	G _i (cAMP modulation) Decrease voltage-sensitive Ca ²⁺ channels (N-, Q-type) Increase K ⁺ _{ir} and K ⁺ A conductance	G _i (cAMP modulation)
RADIOLIGANDS OF CHOICE	[³ H]-CP-55,940, [³ H]-WIN 55,212-2, [³ H]-SR 141716A, [³ H]-HU 243	[³ H]-CP-55,940, [³ H]-WIN 55,212-2, [³ H]-HU 243
TISSUE EXPRESSION	Brain (cerebellum, basal ganglia, cerebral cortex)	Peripheral and central immune cells, sparse in brain
PHYSIOLOGICAL FUNCTION	Activation of presynaptic heteroreceptors to inhibit neurotransmitter release	Suppression of immune cell function
DISEASE RELEVANCE	Pain, appetite regulation, anxiety, depression, emesis muscle spasms, cravings	Pain, immune system regulation

Abbreviations

ACEA: (all Z)-N-(2-Cycloethyl)-5,8,11,14-eicosatetraenamide
AM251: N-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide
AM630: 6-Iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl] (4-methoxyphenyl) methanone
AM281: N-(Morpholin-4-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-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-Δ⁸-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-Δ⁸-tetrahydrocannabinol
LY-320135: 4-[6-Methoxy-2-(4-methoxy-phenyl)-benzofuran-3-carbonyl]-benzotrile
O-1812: (R)-(20-Cyano-16,16-dimethyl docosa-cis-5,8,11,14-tetraeno)-1'-hydroxy-2'-propylamine
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)-1-(4-methoxybenzyl)-pyrazole-3-carboxamide
Δ⁹-THC: Δ⁹-Tetrahydrocannabinol
WIN 55,212-2: [2,3-Dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-yl]-1-(1-naphthalenyl)methanone