Cannabinoid

Overview: Cannabinoid receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Cannabinoid Receptors; see Howlett *et al*., 2002) are activated by endogenous ligands that include *N*-arachidonoylethanolamine (anandamide), *N*-homo-γ-linolenoylethanolamine, *N*-docosatetra-7,10,13,16-enoylethanolamine and 2-arachidonoylglycerol. Potency determinations are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion (see Alexander and Kendall, 2007). Both CB_1 and CB_2 receptors may be labelled with [^{3}H]-CP55940 (0.6 nM; Showalter *et al*., 1996) and [^{3}H]-WIN55212-2 (2–12 nM; Slipetz *et al*., 1995; Song and Bonner, 1996).

Further cannabinoid-like receptors have been described, including GPR55 (ENSG00000135898), which appears to respond to a wide spectrum of cannabinoid agonists and antagonists (see Brown, 2007; Pertwee, 2007; Ryberg *et al*. 2007; Ross, 2009). GPR18 has been described to be a 7-transmembrane receptor for *N*-arachidonoylglycine (Kohno *et al*., 2006), while GPR119 responds to fatty acid ethanolamides (*N*-oleoylethanolamine > *N*-palmitoylethanolamine > anandamide; Overton *et al*., 2006). Synthetic agonists for this receptor include PSN375963 and PSN632408 (Overton *et al*., 2006). Other pharmacological targets for cannabinoids have also been proposed (see Baker *et al*., 2006; Begg *et al*., 2005; Oz, 2006; Pertwee, 2005a).

Nomenclature	CB_1	CB_2
Ensembl ID	ENSG00000118432	ENSG00000162562
Principal transduction	$G_{i/o}$	$G_{i/o}$
Selective agonists	ACEA (Hillard *et al*., 1999), ACPA (Hillard *et al*., 1999), methanandamide (Khanolkar *et al*., 1996), O1812 (Di Marzo *et al*., 2001)	HU308 (Hanus *et al*., 1999), JWH133 (Huffman *et al*., 1999; Pertwee, 2000), L759633 (Ross *et al*., 1999), L759656 (Ross *et al*., 1999), AM1241 (Ibrahim *et al*., 2003)
Selective antagonists	AM251 (8.1, Lan *et al*., 1999a), AM281 (7.9, Lan *et al*., 1999), rimonabant (7.9, Showalter *et al*., 1996), LY320135 (6.9, Felder *et al*., 1998)	SR144528 (9.2, Rinaldi-Carmona *et al*., 1998), AM630 (7.5, Ross *et al*., 1999)
Probes	[^{3}H]-rimonabant (0.6 nM, Rinaldi-Carmona *et al*., 1996)	–

Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs (see O'Sullivan, 2007; Zygmunt *et al*., 1999). There is evidence for an allosteric site on the CB_1 receptor (Price *et al*., 2005). All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems (see Pertwee, 2005a,b).

Abbreviations: **ACEA**, arachidonoyl-2-chloroethylamide; **ACPA**, arachidonoylcyclopropylamide; **AM1241**, (2-iodo-5-nitro-phenyl)-[1-(1-methyl-piperidin-2-ylmethyl)-1*H*-indol-3-yl]-methanone; **AM251**, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; **AM281**, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-4-morpholinyl-1*H*-pyrazole-3-carboxamide; **AM630**, 6-iodopravadoline; **CP55940**, (1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl) phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol; **HU308**, {4-[4-(1,1-dimethylheptyl)-2,6-dimethoxy-phenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl}-methanol; **JWH133**, (3-(1,1-dimethylbutyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromene; **L759633**, (6a*r*,10a*r*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; **L759656**, (6a*r*,10a*r*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6-dimethyl-9-methylene-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene; **LY320135**, (6-methoxy-2-[4-methoxyphenyl]benzo[b]thien-3-yl)(4-cyanophenyl)methanone; **methanandamide**, (*R*)-(+)-arachidonoyl-1'-hydroxy-2'-propylamide; **O1812**, (*R*)-(20-cyano-16,16-dimethyldocosa-*cis*-5,8,11,14-tetraenoyl)-1'-hydroxy-2'-propylamine; **PSN375963**, 4-(5-[4-butylcyclohexyl]-1,2,4-oxadiazol-3-yl)pyridine; **PSN632408**, 4-([3-{4-pyridinyl}-1,2,4-oxadiazol-5-yl]methoxy)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester; **rimonabant**, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride, also known as SR141716A; **SR144528**, *N*-([1*S*]-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; **WIN55212-2**, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate

Further Reading

Alexander SPH, Kendall DA (2007). The complications of promiscuity: endocannabinoid action and metabolism. *Br J Pharmacol* **152**: 602–623.

Baker D, Pryce G, Davies WL, Hiley CR (2006). In silico patent searching reveals a new cannabinoid receptor. *Trends Pharmacol Sci* **27**: 1–4.

Begg M, Pacher P, Batkai S, Osei-Hyiaman D, Offertaler L, Mo FM *et al*. (2005). Evidence for novel cannabinoid receptors. *Pharmacol Ther* **106**: 133–145.

Brown AJ (2007). Novel cannabinoid receptors. *Br J Pharmacol* **152**: 567–575.

Centonze D, Finazzi-Agro A, Bernardi G, Maccarrone M (2007). The endocannabinoid system in targeting inflammatory neurodegenerative diseases. *Trends Pharmacol Sci* **28**: 180–187.

Di Marzo V, De Petrocellis L (2006). Plant, synthetic, and endogenous cannabinoids in medicine. *Annu Rev Med* **57**: 553–574.

Di Marzo V, Bisogno T, De Petrocellis L (2007). Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. *Chem Biol* **14**: 741–756.

Di Marzo V, Petrosino S (2007). Endocannabinoids and the regulation of their levels in health and disease. *Curr Opin Lipidol* **18**: 129–140.

Fernandez-Ruiz J, Romero J, Velasco G, Tolon RM, Ramos JA, Guzman M (2007). Cannabinoid CB_2 receptor: a new target for controlling neural cell survival? *Trends Pharmacol Sci* **28**: 39–45.

Fowler CJ (2006). The cannabinoid system and its pharmacological manipulation – a review, with emphasis upon the uptake and hydrolysis of anandamide. *Fundam Clin Pharmacol* **20**: 549–562.

Harkany T, Guzman M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K (2007). The emerging functions of endocannabinoid signaling during CNS development. *Trends Pharmacol Sci* **28**: 83–92.

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA *et al*. (2002). International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* **54**: 161–202.
Lever IJ, Rice AS (2007). Cannabinoids and pain. *Handb Exp Pharmacol* **177**: 265–306.
Mackie K (2006). Cannabinoid receptors as therapeutic targets. *Annu Rev Pharmacol Toxicol* **46**: 101–122.
McPartland JM, Glass M, Pertwee RG (2007). Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences. *Br J Pharmacol* **152**: 583–593.
O'Sullivan SE (2007). Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol* **152**: 583–593.
Pertwee RG (2005a). Pharmacological actions of cannabinoids. *Handb Exp Pharmacol* **168**: 1–51.
Pertwee RG (2005b). Inverse agonism and neutral antagonism at cannabinoid CB_1 receptors. *Life Sci* **76**: 1307–1324.
Pertwee RG (2006). Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol* **147**: S163–S171.
Pertwee RG (2006). The pharmacology of cannabinoid receptors and their ligands: an overview. *Int J Obes (Lond)* **30**: S13–S18.
Pertwee RG (2007). GPR55: a new member of the cannabinoid receptor clan? *Br J Pharmacol* **152**: 984–986.
Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson N-O, Leonova J *et al*. (2007). The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* **152**: 1092–1110.
Sugiura T, Kishimoto S, Oka S, Gokoh M (2006). Biochemistry, pharmacology and physiology of 2-arachidonoylglycerol, an endogenous cannabinoid receptor ligand. *Prog Lipid Res* **45**: 405–446.
van Diepen H, Schlicker E, Michel MC (2008). Prejunctional and peripheral effects of the cannabinoid CB_1 receptor inverse agonist rimonabant (SR 141716). *Naunyn Schmiedebergs Arch Pharmacol* **378**: 345–369.

References

Di Marzo V *et al*. (2001). *Biochem Biophys Res Commun* **281**: 444–451.
Felder CC *et al*. (1998). *J Pharmacol Exp Ther* **284**: 291–297.
Hanus L *et al*. (1999). *Proc Natl Acad Sci USA* **96**: 14228–14233.
Hillard CJ *et al*. (1999). *J Pharmacol Exp Ther* **289**: 1427–1433.
Huffman JW *et al*. (1999). *Bioorg Med Chem* **7**: 2905–2914.
Ibrahim MM *et al*. (2003). *Proc Natl Acad Sci USA* **100**: 10529–10533.
Khanolkar AD *et al*. (1996). *J Med Chem* **39**: 4515–4519.
Kohno M *et al*. (2006). *Biochem Biophys Res Commun* **347**: 827–832.
Lan R *et al*. (1999). *AAPS PharmSci* **1**: E4
Lan RX *et al*. (1999a). *J Med Chem* **42**: 769–776.
Overton HA *et al*. (2006). *Cell Metab* **3**: 167–175.
Pertwee RG (2000). *Expert Opin Investig Drugs* **9**: 1553–1571.
Price MR *et al*. (2005). *Mol Pharmacol* **68**: 1484–1495.
Rinaldi-Carmona M *et al*. (1996). *Life Sci* **58**: 1239–1247.
Rinaldi-Carmona M *et al*. (1998). *J Pharmacol Exp Ther* **284**: 644–650.
Ross RA *et al*. (1999). *Br J Pharmacol* **126**: 665–672.
Ross RA (2009). *Trends Pharmacol Sci* **30**: 156–163.
Showalter VM *et al*. (1996). *J Pharmacol Exp Ther* **278**: 989–999.
Slipetz DM *et al*. (1995). *Mol Pharmacol* **48**: 352–361.
Song ZH, Bonner TI (1996). *Mol Pharmacol* **49**: 891–896.
Zygmunt PM *et al*. (1999). *Nature* **400**: 452–457.