11-10-09 #10

2091 San Francisco Ave.
Long Beach, CA 90806
Tel: (562) 599-0812

Memo

To: The Honorable Mayor Foster and Members of the City Council

From: Joan Greenwood JGA

Date: November 10, 2009

Re: Agenda Item Number 10 (09-1203): Draft Ordinance Regulating Medical Marijuana

---

My purpose in coming before you this evening is to bring the discussion back to the scientific realm. While a graduate student in chemistry at Northeastern University, I took a course taught by Dr. Ralph Mechoulam, an internationally known expert on psychitomimetic properties of cannabinoids.

As a scientist, there is no doubt in my mind that the verifiable benefits of medical marijuana exist and that despite decades of research, no synthetic drug matches its performance in terms of efficacy and safety. Yet, the debate surrounding this ordinance appears to focus on prevention of illegal use not serving the needs of the medical community.

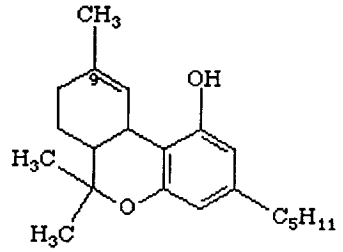
I have attached a collection of abstracts of scientific studies demonstrating that attempts to find beneficial analogs of cannabinoids found in marijuana are extensive and largely unsuccessful. Nabilone and dronabinol, which are available legally, have much more severe side effects and high abuse liability which limits their medical use. In other words, the drug analogs available legally to patients have more serious consequences than medical marijuana. (***Pharmacology and Toxicology of Cannabis Derivatives and Endocannabinoid Agonists***. Health and Human Development Section, United Nations Office on Drugs and Crime, Vienna, Italy.)

Pharmacology of Tetrahydrocannabinol

[Chemical Comparison Table | Hemp Page]

Tetrahydrocannabinol (THC) was first isolated from hemp in 1965. THC's intoxicating and medicinal properties have been touted for thousands of years; however, use of the substance is highly controlled in the U.S. and in some other countries.

tetrahydrocannabinol



Delta-trans-tetrahydrocannabinol, in capsule form more commonly known as dronabinol and sold as Marinol by Roxane Laboratories, is federally recognized as an appetite stimulant and anti-nausea/vomiting (antiemetic) agent (though some research indicates it is useful as an anti-**glaucoma** agent as well). It is available only through special prescription to treat persons suffering from chemotherapy- or radiation-related nausea, and to treat people suffering from **AIDS**-related anorexia. The FDA approved it for use as an antiemetic for chemotherapy patients in 1985 and as an appetite stimulant for AIDS patients in 1992.

Dronabinol has a complicated effect on the **central nervous system**, but it basically suppresses the neural impulses associated with nausea and stimulates the appetite (sometimes quite dramatically). As an appetite stimulant, a typical effective dose is 5 milligrams/day (2.5 mg an hour before lunch and dinner), though in clinical trials the dose ranged from 2.5-20 mg/day. As an antiemetic, total daily dosages range from 2.5-40 mg/day. Antiemetic doses are administered every four to six hours and seem to work best for people undergoing chemotherapy for **lymphoma**. Doctors can also obtain and prescribe federally-rolled marijuana cigarettes for patients who are too sick to keep down pills.

Side effects of dronabinol can include sleepiness, dizziness, confusion, and rapid heartbeat. Severe overdoses can cause panic attacks, seizures in epileptics, and possibly hallucinations. Long-term use can possibly result in psychological addiction. Abrupt discontinuation of the drug can cause symptoms such as irritability, insomnia and sweating. In animal studies, dronabinol caused stillbirths and pup mortality, so it's recommended that pregnant women avoid the drug.

This information is for educational use only. People should not attempt to medicate themselves with THC or with any of the other drugs listed in Cyberbotanica. Possession of unprescribed THC is illegal in the U.S. and many other countries.

For more information, visit:

- NCI Fact Sheet: Marijuana Use in Supportive Care for Cancer Patients
- Marinol (dronabinol) Fact Sheet
- Marinol Product Information from Roxane
- NIH Information on 1-Trans-Delta-9-Tetrahydrocannabinol
- Toxicology and Carcinogenesis Studies of 1-Trans-Delta9-Tetrahydrocannabinol

References:

Budavari, Susan, ed. 1989. *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals.* Rahway, NJ, Merck & Co.

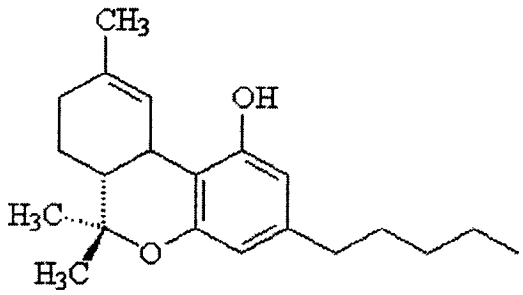
1995 Physician's Desk Reference ©. Montvale, NJ, Medical Economics Data Production Company.

BioTech | Cyberbotanica HOME PAGE | WORKS CITED/ WWW LINKS | TEST YOURSELF

Tetrahydrocannabinol - THC

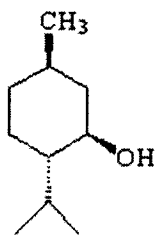
Tetrahydrocannabinol (THC) is the active chemical in *cannabis* and is one of the oldest hallucinogenic drugs known. There is evidence that cannabis extracts were used by the Chinese as a herbal remedy since the first century AD. Cannabis comes from the flowering tops and leaves of the hemp plant, *Cannabis sativa* (shown in the picture on the right). For centuries this plant has been widely cultivated around the world for its fibres, and indeed the word *canvas*, which is a material made from woven hemp fibres, takes its name from cannabis. However, cannabis is more commonly known as the source of the *marijuana* drug, although the word *marijuana* applies both to the whole plant, and to the resin from it (although this is sometimes also called *hashish*).

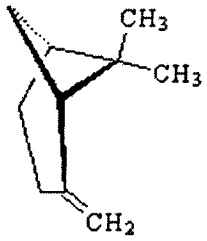
Cannabis contains approximately 60 different psychoactive chemicals called cannabinoids, of which the most important one is tetrahydrocannabinol (THC). The mode of action of THC is still not properly understood, although it is known that of the two stereoisomers (mirror images), the (-)-form (the left-handed form of the molecule) is 10-15 times more potent than the (+)-form.

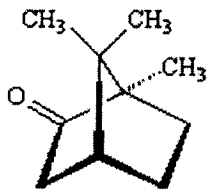


THC - the active component of cannabis

The cannabinoids belong to a class of chemicals called terpenoids, meaning terpene-like. These compounds occur as essential oils within many plants and some are involved in the formation of vitamins, steroids, pigments and odours. The perfume industry relies on compounds such as these, and they also find a variety of uses in the food and pharmaceutical industry as flavour and odour improvers. Terpenes can be linear (such as geraniol or citronella) or cyclic as in THC. Examples of some other simple cyclic terpenes are shown below.







menthol (peppermint oil)	**b-pinene** (turpentine)	**Camphor** (from the camphor tree)

THC as an Illegal Drug

The cannabinoids are basically non-polar molecules, with low solubility in water, so they are normally self-administered by smoking. The volatilised fractions are inhaled as a vapour and give rise to a number of physiological effects. These effects depend very much upon the expectations and mood of the user, the quantity taken, and the possible presence of other drugs (such as alcohol) in the body. Generally people experience a pleasurable state of relaxation, with heightened sensory experiences of taste, sound and colour. Repeated experiments have failed to show any short term dangers, although it hasn't been proven to be 'safe' in the pharmacological sense either. THC is non-addictive and there are no withdrawal symptoms. However, one of the side-effects of its use is to make the user drowsy, with reduced concentration and short term memory. As a result, it was made illegal in the UK for recreational use in 1928, although it is still legal in a number of other countries.

Medical Uses

Apart from the recreational uses and abuses, THC does have some medical uses. Its anti-emetic properties (inhibits vomiting) are particularly useful in the treatment of cancer patients on chemotherapy. Also, as THC increases the appetite and reduces the vomit response, it is starting to be used in the treatment of anorexia and other eating disorders.

References:

- *Organic Chemistry*, Morrison and Boyd (Allyn and Bacon, 1983).
- *Biochemistry*, L. Stryer (W.H. Freeman and Co, San Francisco, 1975).
- *Molecules*, P.W. Atkins (W.H. Freeman and Co, New York, 1987)

Forsch Komplementarmed. 1999 Oct ;6 Suppl 3 :12-5 10575283 (P,S,G,E,B)
[Cited?]
Cannabis and cannabinoids: pharmacology and rationale for clinical use.
R G Pertwee
Institute of Biomedical Sciences, Aberdeen, Scotland. rgp@aberdeen.ac.uk
It is now known that there are at least two types of cannabinoid receptors. These are CB1 receptors, present mainly on central and peripheral neurones, and CB2 receptors, present mainly on immune cells. Endogenous cannabinoid receptor agonists ('endocannabinoids') have also been identified. The discovery of this 'endogenous cannabinoid system' has led to the development of selective CB1 and CB2 receptor ligands and fueled renewed interest in the clinical potential of cannabinoids. Two cannabinoid CB1 receptor agonists are already used clinically, as antiemetics or as appetite stimulants. These are D 9 - tetrahydrocannabinol (THC) and nabilone. Other possible uses for CB1 receptor agonists include the suppression of muscle spasm/spasticity associated with multiple sclerosis or spinal cord injury, the relief of chronic pain and the management of glaucoma and bronchial asthma. CB1 receptor antagonists may also have clinical applications, e. g. as appetite suppressants and in the management of schizophrenia or disorders of cognition and memory. So too may CB2 receptor ligands and drugs that activate cannabinoid receptors indirectly by augmenting endocannabinoid levels at cannabinoid receptors. When taken orally, THC seems to undergo variable absorption and to have a narrow 'therapeutic window'(dose range in which it is effective without producing significant unwanted effects). This makes it difficult to predict an oral dose that will be both effective and tolerable to a patient and indicates a need for better cannabinoid formulations and modes of administration. For the therapeutic potential of cannabis or CB1 receptor agonists to be fully exploited, it will be important to establish objectively and conclusively (a) whether these agents have efficacy against selected symptoms that is of clinical significance and, if so, whether the benefits outweigh the risks,(b) whether cannabis has therapeutic advantages over individual cannabinoids,(c) whether there is a need for additional drug treatments to manage any of the disorders against which cannabinoids are effective, and (d) whether it will be possible to develop drugs that have reduced psychotropic activity and yet retain the ability to act through CB1 receptors to produce their sought-after effects.
Mesh-terms: Antiemetics :: therapeutic use; Appetite Stimulants :: therapeutic use; Cannabinoids :: pharmacology; Cannabinoids :: therapeutic use; Cannabis :: therapeutic use; Endocannabinoids; Human; Phytotherapy; Receptors, Cannabinoid; Receptors, Drug :: classification; Receptors, Drug :: physiology; Tetrahydrocannabinol :: analogs & derivatives; Tetrahydrocannabinol :: therapeutic use;
[Show abstracts]

Other papers by authors:

Br J Pharmacol. 2007 Sep 17;: 17876300 (P,S,G,E,B,D) Cited:26
[Cited?]
GPR55: a new member of the cannabinoid receptor clan?
R G Pertwee
In this issue of the British Journal of Pharmacology, Ryberg et al. present convincing in vitro evidence that the orphan GPCR, GPR55, is a cannabinoid receptor. GPR55 was activated by a

range of plant, synthetic and endogenous cannabinoids and blocked by the non-psychoactive phytocannabinoid, cannabidiol. Their experiments have revealed several differences between the pharmacology of GPR55 and the established cannabinoid CB(1) and CB(2) receptors. For example, the CB(1) receptor antagonist, AM251, activated GPR55 and the main psychoactive constituent of cannabis, Delta(9)-tetrahydrocannabinol, displayed greater efficacy at GPR55 than at CB(1) or CB(2) receptors. They also compared the distribution of GPR55 and CB(1) mRNA in mouse and report that GPR55 couples to Galpha(13), that it is activated by virodhamine, palmitoylethanolamide and oleoylethanolamide, and that virodhamine displays relatively high efficacy as a GPR55 agonist. Still to be identified are the main roles played by GPR55 in health and disease and any potential therapeutic benefits of activating or blocking this receptor.British Journal of Pharmacology advance online publication, 17 September 2007; doi:10.1038/sj.bjp.0707464.

Br J Pharmacol. 2007 Sep 10;: 17828291 (P,S,G,E,B,D) Cited:9

[Cited?]

The diverse CB(1) and CB(2) receptor pharmacology of three plant cannabinoids: Delta(9)-tetrahydrocannabinol, cannabidiol and Delta(9)-tetrahydrocannabivarin.

R G Pertwee

Cannabis sativa is the source of a unique set of compounds known collectively as plant cannabinoids or phytocannabinoids. This review focuses on the manner with which three of these compounds,(-)-trans-Delta(9)-tetrahydrocannabinol (Delta(9)-THC),(-)-cannabidiol (CBD) and (-)-trans-Delta(9)-tetrahydrocannabivarin (Delta(9)-THCV), interact with cannabinoid CB(1) and CB(2) receptors. Delta(9)-THC, the main psychotropic constituent of cannabis, is a CB(1) and CB(2) receptor partial agonist and in line with classical pharmacology, the responses it elicits appear to be strongly influenced both by the expression level and signalling efficiency of cannabinoid receptors and by ongoing endogenous cannabinoid release. CBD displays unexpectedly high potency as an antagonist of CB(1)/CB(2) receptor agonists in CB(1)- and CB(2)-expressing cells or tissues, the manner with which it interacts with CB(2) receptors providing a possible explanation for its ability to inhibit evoked immune cell migration. Delta(9)-THCV behaves as a potent CB(2) receptor partial agonist in vitro. In contrast, it antagonizes cannabinoid receptor agonists in CB(1)-expressing tissues. This it does with relatively high potency and in a manner that is both tissue and ligand dependent. Delta(9)-THCV also interacts with CB(1) receptors when administered in vivo, behaving either as a CB(1) antagonist or, at higher doses, as a CB(1) receptor agonist. Brief mention is also made in this review, first of the production by Delta(9)-THC of pharmacodynamic tolerance, second of current knowledge about the extent to which Delta(9)-THC, CBD and Delta(9)-THCV interact with pharmacological targets other than CB(1) or CB(2) receptors, and third of actual and potential therapeutic applications for each of these cannabinoids.British Journal of Pharmacology advance online publication, 10 September 2007; doi:10.1038/sj.bjp.0707442.

Br J Pharmacol. 2007 Jul 16;: 17641667 (P,S,G,E,B,D) Cited:7

[Cited?]

Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences.

J M McPartland, M Glass, R G Pertwee

A meta-analysis, unlike a literature review, synthesizes previous studies into new results. Pooled data from 211 studies measured ligand binding affinities at human (Hs) or rat (Rn) cannabinoid receptors CB(1) and CB(2). Cochrane methods were modified for this non-clinical analysis.

Meta-regression detected data heterogeneity arising from methodological factors: use of sectioned tissues, lack of PMSF and choice of radioligand. Native brain tissues exhibited greater affinity (lower nM) than transfected cells, but the trend fell short of significance, as did the trend between centrifugation and filtration methods. Correcting for heterogeneity, mean K(i) values for Delta(9)-tetrahydrocannabinol differed significantly between HsCB(1) and RnCB(1)(25.1 and 42.6 nM, respectively) but not between HsCB(1) and HsCB(2)(25.1 and 35.2). Mean K(d) values for HsCB(1), RnCB(1) and HsCB(2) of CP55,940 (2.5, .98, .92) and WIN55,212-2 (16.7, 2.4, 3.7) differed between HsCB(1) and RnCB(1) and between HsCB(1) and HsCB(2). SR141716A differed between HsCB(1) and RnCB(1)(2.9 and 1. nM). Anandamide at HsCB(1), RnCB(1) and HsCB(2)(239.2, 87.7, 439.5) fell short of statistical differences due to heterogeneity. We consider these K(d) and K(i) values to be the most valid estimates in the literature. Sensitivity analyses did not support the numerical validity of cannabidiol, cannabinol, 2-arachidonoyl glycerol and all ligands at RnCB(2). Aggregate rank order analysis of CB(1) distribution in the brain (pooled from 119 autoradiographic, immunohistochemical and in situ hybridization studies) showed denser HsCB(1) expression in cognitive regions (cerebral cortex) compared to RnCB(1), which was relatively richer in movement-associated areas (cerebellum, caudate-putamen). Implications of interspecies differences are discussed.British Journal of Pharmacology advance online publication, 16 July 2007; doi:10.1038/sj.bjp.0707399.
Br J Pharmacol. 2007 May 14;: 17502849 (P,S,G,E,B,D)
[Cited?]

The synthetic cannabinoid HU210 induces spatial memory deficits and suppresses hippocampal firing rate in rats.

L Robinson, A V Goonawardena, R G Pertwee, R E Hampson, G Riedel
1Department of Biomedical Sciences, Institute for Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK.

Background and purpose:Previous work implied that the hippocampal cannabinoid system was particularly important in some forms of learning, but direct evidence for this hypothesis is scarce. We therefore assessed the effects of the synthetic cannabinoid HU210 on memory and hippocampal activity.Experimental approach:HU210 (100 mug kg(-1)) was administered intraperitoneally to rats under three experimental conditions. One group of animals were pre-trained in spatial working memory using a delayed-matching-to-position task and effects of HU210 were assessed in a within-subject design. In another, rats were injected before acquisition learning of a spatial reference memory task with constant platform location. Finally, a separate group of animals was implanted with electrode bundles in CA1 and CA3 and single unit responses were isolated, before and after HU210 treatment.Key results:HU210 treatment had no effect on working or short-term memory. Relative to its control Tween 80, deficits in acquisition of a reference memory version of the water maze were obtained, along with drug-related effects on anxiety, motor activity and spatial learning. Deficits were not reversed by the CB(1) receptor antagonists SR141716A (3 mg kg(-1)) or AM281 (1.5 mg kg(-1)). Single unit recordings from principal neurons in hippocampal CA3 and CA1 confirmed HU210-induced attenuation of the overall firing activity lowering both the number of complex spikes fired and the occurrence of bursts.Conclusions and implications:These data provide the first direct evidence that the underlying mechanism for the spatial memory deficits induced by HU210 in rats is the accompanying abnormality in hippocampal cell firing.British Journal of Pharmacology advance online publication, 14 May 2007; doi:10.1038/sj.bjp.0707273.
Br J Pharmacol. 2007 Jan 22;: 17245367 (P,S,G,E,B,D) Cited:5

[Cited?]
The psychoactive plant cannabinoid, Delta(9)-tetrahydrocannabinol, is antagonized by Delta(8)- and Delta(9)-tetrahydrocannabivarin in mice in vivo.
R G Pertwee, A Thomas, L A Stevenson, R A Ross, S A Varvel, A H Lichtman, B R Martin, R K Razdan
1School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK.
Background and purpose:To follow up in vitro evidence that Delta(9)-tetrahydrocannabivarin extracted from cannabis (eDelta(9)-THCV) is a CB(1) receptor antagonist by establishing whether synthetic Delta(9)-tetrahydrocannabivarin (O-4394) and Delta(8)-tetrahydrocannabivarin (O-4395) behave as CB(1) antagonists in vivo.Experimental approach:O-4394 and O-4395 were compared with eDelta(9)-THCV as displacers of [(3)H]-CP55940 from specific CB(1) binding sites on mouse brain membranes and as antagonists of CP55940 in [(35)S]GTPgammaS binding assays performed with mouse brain membranes and of R-(+)-WIN55212 in mouse isolated vasa deferentia. Their ability to antagonize in vivo effects of 3 or 10 mg kg(-1)(i.v.) Delta(9)-tetrahydrocannabinol in mice was then investigated.Key results:O-4394 and O-4395 exhibited similar potencies to eDelta(9)-THCV as displacers of [(3)H]-CP55940 (K (i)=46.6 and 64.4 nM, respectively) and as antagonists of CP55940 in the [(35)S]GTPgammaS binding assay (apparent K (B)=82.1 and 125.9 nM, respectively) and R-(+)-WIN55212 in the vas deferens (apparent K (B)=4.8 and 3.9 nM respectively). At i.v. doses of .1, .3, 1. and/or 3 mg kg(-1) O-4394 and O-4395 attenuated Delta(9)-tetrahydrocannabinol-induced anti-nociception (tail-flick test) and hypothermia (rectal temperature). O-4395 but not O-4394 also antagonized Delta(9)-tetrahydrocannabinol-induced ring immobility. By themselves, O-4395 and O-4394 induced ring immobility at 3 or 10 mg kg(-1)(i.v.) and antinociception at doses above 10 mg kg(-1)(i.v.). O-4395 also induced hypothermia at 3 mg kg(-1)(i.v.) and above.Conclusions and implications:O-4394 and O-4395 exhibit similar in vitro potencies to eDelta(9)-THCV as CB(1) receptor ligands and as antagonists of cannabinoid receptor agonists and can antagonize Delta(9)-tetrahydrocannabinol in vivo.British Journal of Pharmacology advance online publication, 22 January 2007; doi:10.1038/sj.bjp.0707124.
Br J Pharmacol. 2007 Jan 22;: 17245363 (P,S,G,E,B,D) Cited:28
[Cited?]
Cannabidiol displays unexpectedly high potency as an antagonist of CB(1) and CB(2) receptor agonists in vitro.
A Thomas, G L Baillie, A M Phillips, R K Razdan, R A Ross, R G Pertwee
1School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK.
Background and purpose:A nonpsychoactive constituent of the cannabis plant, cannabidiol has been demonstrated to have low affinity for both cannabinoid CB(1) and CB(2) receptors. We have shown previously that cannabidiol can enhance electrically evoked contractions of the mouse vas deferens, suggestive of inverse agonism. We have also shown that cannabidiol can antagonize cannabinoid receptor agonists in this tissue with a greater potency than we would expect from its poor affinity for cannabinoid receptors. This study aimed to investigate whether these properties of cannabidiol extend to CB(1) receptors expressed in mouse brain and to human CB(2) receptors that have been transfected into CHO cells.Experimental approach:The [(35)S]GTPgammaS binding assay was used to determine both the efficacy of cannabidiol and the ability of cannabidiol to antagonize cannabinoid receptor agonists (CP55940 and R-(+)-

WIN55212) at the mouse CB(1) and the human CB(2) receptor.Key results:This paper reports firstly that cannabidiol displays inverse agonism at the human CB(2) receptor. Secondly, we demonstrate that cannabidiol is a high potency antagonist of cannabinoid receptor agonists in mouse brain and in membranes from CHO cells transfected with human CB(2) receptors.Conclusions and implications:This study has provided the first evidence that cannabidiol can display CB(2) receptor inverse agonism, an action that appears to be responsible for its antagonism of CP55940 at the human CB(2) receptor. The ability of cannabidiol to behave as a CB(2) receptor inverse agonist may contribute to its documented anti-inflammatory properties.British Journal of Pharmacology advance online publication, 22 January 2007; doi:10.1038/sj.bjp.0707133.

Handb Exp Pharmacol. 2005 ;(168):1-51 16596770 (P,S,G,E,B)

[Cited?]

Pharmacological actions of cannabinoids.

R G Pertwee

School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK. rgp@abdn.ac.uk

Mammalian tissues express at least two types of cannabinoid receptor, CB1 and CB2, both G protein coupled. CB1 receptors are expressed predominantly at nerve terminals where they mediate inhibition of transmitter release. CB2 receptors are found mainly on immune cells, one of their roles being to modulate cytokine release. Endogenous ligands for these receptors (endocannabinoids) also exist. These are all eicosanoids; prominent examples include arachidonoylethanolamide (anandamide) and 2-arachidonoyl glycerol. These discoveries have led to the development of CB1- and CB2-selective agonists and antagonists and of bioassays for characterizing such ligands. Cannabinoid receptor antagonists include the CB1-selective SR141716A, AM251, AM281 and LY320135, and the CB2-selective SR144528 and AM630. These all behave as inverse agonists, one indication that CB1 and CB2 receptors can exist in a constitutively active state. Neutral cannabinoid receptor antagonists that seem to lack inverse agonist properties have recently also been developed. As well as acting on CB1 and CB2 receptors, there is convincing evidence that anandamide can activate transient receptor potential vanilloid type 1 (TRPV1) receptors. Certain cannabinoids also appear to have non-CB1, non-CB2, non-TRPV1 targets, for example CB2-like receptors that can mediate antinociception and "abnormal-cannabidiol" receptors that mediate vasorelaxation and promote microglial cell migration. There is evidence too for TRPV1-like receptors on glutamatergic neurons, for alpha2-adrenoceptor-like (imidazoline) receptors at sympathetic nerve terminals, for novel G protein-coupled receptors for R-(+)-WIN55212 and anandamide in the brain and spinal cord, for novel receptors for delta9-tetrahydrocannabinol and cannabinol on perivascular sensory nerves and for novel anandamide receptors in the gastro-intestinal tract. The presence of allosteric sites for cannabinoids on various ion channels and non-cannabinoid receptors has also been proposed. In addition, more information is beginning to emerge about the pharmacological actions of the non-psychoactive plant cannabinoid, cannabidiol. These recent advances in cannabinoid pharmacology are all discussed in this review.

Int J Obes (Lond). 2006 Apr ;30 Suppl 1 :S13-8 16570099 (P,S,G,E,B,D) Cited:12

[Cited?]

The pharmacology of cannabinoid receptors and their ligands: an overview.

R G Pertwee

1School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland, UK.
Mammalian tissues express at least two cannabinoid receptor types, CB(1) and CB(2), both G protein coupled. CB(1) receptors are found predominantly at nerve terminals where they mediate inhibition of transmitter release. CB(2) receptors occur mainly on immune cells, one of their roles being to modulate cytokine release. Endogenous agonists for cannabinoid receptors also exist, and are all eicosanoids. The first-discovered of these 'endocannabinoids' was arachidonoylethanolamide and there is convincing evidence that this ligand and some of its metabolites can activate vanilloid VRI (TRPV1) receptors. Certain cannabinoids also appear to have TRPV1-like and/or non-CB(1), non-CB(2), non-TRPV1 targets. Several CB(1)- and CB(2)-selective agonists and antagonists have been developed. Antagonists include the CB(1)-selective SR141716A, AM251, AM281 and LY320135, and the CB(2)-selective SR144528 and AM630. These all behave as inverse agonists, one indication that CB(1) and CB(2) receptors can exist in a constitutively active state. 'Neutral' cannabinoid receptor antagonists have also been developed. CB(1) and/or CB(2) receptor activation appears to ameliorate inflammatory and neuropathic pain and certain multiple sclerosis symptoms. This might be exploited clinically by using CB(1), CB(2) or CB(1)/CB(2) agonists, or inhibitors of the membrane transport or catabolism of endocannabinoids that are released in increased amounts, at least in animal models of pain and multiple sclerosis. We have recently discovered the presence of an allosteric site on the CB(1) receptor. Consequently, it may also prove possible to enhance 'autoprotective' effects of released endocannabinoids with CB(1) allosteric enhancers or, indeed, to reduce proposed 'autoimpairing' effects of released endocannabinoids such as excessive food intake with CB(1) allosteric antagonists.International Journal of Obesity (2006) 30, S13-S18. doi:10.1038/sj.ijo.0803272.
Bull Exp Biol Med. 2005 May ;139:558-61 16224548 (P,S,G,E,B)
[Cited?]
Cannabinoid receptor antagonists SR141716 and SR144528 exhibit properties of partial agonists in experiments on isolated perfused rat heart.
A V Krylatov, L N Maslov, O V Lasukova, R G Pertwee
We studied the effect of selective cannabinoid receptor ligands on contractility of isolated Langendorff-perfused rat heart. It was found that 10-min perfusion of rat heart with a solution containing selective agonist of CB1 and CB2 receptors HU-210 (10 nM) decreased left ventricular developed pressure and maximum rates of contraction and relaxation. However, HU-210 had no effect on heart rate and end-diastolic pressure. Treatment with selective CB1 receptor antagonist SR141716 (1 microM) and selective CB2 receptor antagonist SR144528 (1 microM) decreased left ventricular developed pressure and maximum rates of contraction and relaxation, but had no effect on heart rate and end-diastolic pressure. Ten-minute perfusion of rat heart with a solution containing selective agonist of CB1 and CB2 receptors HU-210 (10 nM) decreased cAMP concentration in the heart. CB receptor antagonists had little effect on cAMP concentration in the heart. The negative inotropic effect of HU-210 and CB receptor antagonists is probably mediated by activation of CB1 receptors. It can be hypothesized that the decrease in heart cAMP concentration is related to stimulation of CB2 receptors. Our results suggest that selective CB receptor antagonists SR141716 and SR144528 in a final concentration of 1 microM exhibit properties of partial CB receptor agonists.
Br J Ophthalmol. 2004 May ;88 (5):708-13 15090428 (P,S,G,E,B)
[Cited?]
Cannabinoids and glaucoma.

I Tomida, R G Pertwee, A Azuara-Blanco
Department of Ophthalmology, Aberdeen Royal Infirmary, University of Aberdeen, UK.
Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, UK.
Glaucoma is one of the leading causes of blindness in the world. In spite of the diverse therapeutic possibilities, new and better treatments for glaucoma are highly desirable. Cannabinoids effectively lower the intraocular pressure (IOP) and have neuroprotective actions. Thus, they could potentially be useful in the treatment of glaucoma. The purpose of this article is to provide the reader with an overview of the latest achievements in research into the potential use of cannabinoids for glaucoma.

Latest similar papers:

Int Rev Neurobiol. 2009 ;88 :335-69 19897083 (P,S,G,E,B,D)
[Cited?]
Cannabinoid receptors in brain: pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications.
Emmanuel S Onaivi
Department of Biology, William Paterson University, Wayne, New Jersey 07470, USA.
Much progress has been achieved in cannabinoid research. A major breakthrough in marijuana-cannabinoid research has been the discovery of a previously unknown but elaborate endogenous endocannabinoid system (ECS), complete with endocannabinoids and enzymes for their biosynthesis and degradation with genes encoding two distinct cannabinoid (CB1 and CB2) receptors (CBRs) that are activated by endocannabinoids, cannabinoids, and marijuana use. Physical and genetic localization of the CBR genes CNR1 and CNR2 have been mapped to chromosome 6 and 1, respectively. A number of variations in CBR genes have been associated with human disorders including osteoporosis, attention deficit hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), drug dependency, obesity, and depression. Other family of lipid receptors including vanilloid (VR1) and lysophosphatidic acid (LPA) receptors appear to be related to the CBRs at the phylogenetic level. The ubiquitous abundance and differential distribution of the ECS in the human body and brain along with the coupling to many signal transduction pathways may explain the effects in most biological system and the myriad behavioral effects associated with smoking marijuana. The neuropharmacological and neuroprotective features of phytocannabinoids and endocannabinoid associated neurogenesis have revealed roles for the use of cannabinoids in neurodegenerative pathologies with less neurotoxicity. The remarkable progress in understanding the biological actions of marijuana and cannabinoids have provided much richer results than previously appreciated cannabinoid genomics and raised a number of critical issues on the molecular mechanisms of cannabinoid induced behavioral and biochemical alterations. These advances will allow specific therapeutic targeting of the different components of the ECS in health and disease. This review focuses on these recent advances in cannabinoid genomics and the surprising new fundamental roles that the ECS plays in the retrograde signaling associated with cannabinoid inhibition of neurotransmitter release to the genetic basis of the effects of marijuana use and pharmacotherpeutic applications and limitations. Much evidence is provided for the complex CNR1 and CNR2 gene structures and their associated regulatory elements. Thus, understanding the ECS in the human body and brain will contribute to elucidating this natural regulatory mechanism in health and disease.

Curr Opin Pharmacol. 2009 Oct 24;: 19857996 (P,S,G,E,B,D)
[Cited?]
Cannabinoid-opioid interactions during neuropathic pain and analgesia.
Ittai Bushlin, Raphael Rozenfeld, Lakshmi A Devi
Department of Pharmacology and Systems Therapeutics, Mount Sinai School of Medicine, New York, NY 10029, United States.
Opiates and exogenous cannabinoids, both potent analgesics used for the treatment of patients with neuropathic pain, bind to and activate class A G-protein-coupled receptors (GPCRs). Several lines of evidence have recently suggested that opioid and cannabinoid receptors can functionally interact in the central nervous system (CNS). These interactions may be direct, such as through receptor heteromerization, or indirect, such as through signaling cross-talk that includes agonist-mediated release and/or synthesis of endogenous ligands that can activate downstream receptors. Interactions between opioid and cannabinoid receptors may mediate many of the behavioral phenomena associated with the use of these drugs, including the production of acute antinociception and the development of tolerance and cross-tolerance to the antinociceptive effects of opioid and cannabinoid-specific ligands. This review summarizes behavioral, anatomical, and molecular data characterizing these interactions during the development of neuropathic pain and during antinociceptive treatment with these drugs alone or in combination. These studies are critical for understanding how the receptor systems involved in pain relief are altered during acute or chronic pain, and for designing better antinociceptive drug therapies, such as the combined use of opioid and cannabinoid receptor agonists or selective activation of receptor heteromers, that directly target the altered neurophysiology of patients experiencing pain.
Inhal Toxicol. 2009 Nov ;21 (13):1108-12 19852551 (P,S,G,E,B,D)
[Cited?]
Cannabis smoke condensate III: The cannabinoid content of vaporised Cannabis sativa.
B Pomahacova, F Van der Kooy, R Verpoorte
Division of Pharmacognosy, Section of Metabolomics, Institute of Biology, Leiden University, Leiden, The Netherlands.
Cannabis sativa is a well-known recreational drug and, as such, a controlled substance of which possession and use are illegal in most countries of the world. Due to the legal constraints on the possession and use of C. sativa, relatively little research on the medicinal qualities of this plant has been conducted. Interest in the medicinal uses of this plant has, however, increased in the last decades. The methods of administration for medicinal purposes are mainly through oral ingestion, smoking, and nowadays also inhalation through vaporization. During this study the commercially available Volcano vaporizing device was compared with cannabis cigarette smoke. The cannabis smoke and vapor (obtained at different temperatures) were quantitatively analyzed by high-performance liquid chromatography (HPLC). In addition, different quantities of cannabis material were also tested with the vaporizer. The cannabinoids:by-products ratio in the vapor obtained at 200 degrees C and 230 degrees C was significantly higher than in the cigarette smoke. The worst ratio of cannabinoids:by-products was obtained from the vaporized cannabis sample at 170 degrees C.
J Neuroimmune Pharmacol. 2009 Oct 22;: 19847654 (P,S,G,E,B,D)
[Cited?]

Non-CB(1), Non-CB(2) Receptors for Endocannabinoids, Plant Cannabinoids, and Synthetic Cannabimimetics: Focus on G-protein-coupled Receptors and Transient Receptor Potential Channels.

Luciano De Petrocellis, Vincenzo Di Marzo
Endocannabinoid Research Group, Institute of Cybernetics, Consiglio Nazionale delle Ricerche, 80078, Pozzuoli, NA, Italy.

The molecular mechanism of action of Delta(9)-tetrahydrocannabinol (THC), the psychotropic constituent of Cannabis, has been a puzzle during the three decades separating its characterization, in 1964, and the cloning, in the 1990s, of cannabinoid CB(1) and CB(2) receptors. However, while these latter proteins do mediate most of the pharmacological actions of THC, they do not seem to act as receptors for other plant cannabinoids (phytocannabinoids), nor are they the unique targets of the endogenous lipids that were originally identified in animals as agonists of CB(1) and CB(2) receptors, and named endocannabinoids. Over the last decade, several potential alternative receptors for phytocannabinoids, endocannabinoids, and even synthetic cannabimimetics, have been proposed, often based uniquely on pharmacological evidence obtained in vitro. In particular, the endocannabinoid anandamide, and the other most abundant Cannabis constituent, cannabidiol, seem to be the most "promiscuous" of these compounds. In this article, we review the latest data on the non-CB(1), non-CB(2) receptors suggested so far for endocannabinoids and plant or synthetic cannabinoids, and lay special emphasis on uncharacterized or orphan G-protein-coupled receptors as well as on transient receptor potential channels.

CNS Neurol Disord Drug Targets. 2009 Oct 19;: 19839937 (P,S,G,E,B)

[Cited?]

The Endocannabinoid System and Pain.

Josée Guindon, Andrea G Hohmann
Neuroscience and Behavior Program, Department of Psychology, University of Georgia, Athens, GA 30602-3013, USA. ahohmann@uga.edu.

The therapeutic potential of cannabinoids has been the topic of extensive investigation following the discovery of cannabinoid receptors and their endogenous ligands. Cannabinoid receptors and their endogenous ligands are present at supraspinal, spinal and peripheral levels. Cannabinoids suppress behavioral responses to noxious stimulation and suppress nociceptive processing through activation of cannabinoid CB1 and CB2 receptor subtypes. Endocannabinoids, the brain's own cannabis-like substances, share the same molecular target as 9-tetrahydrocannabinol, the main psychoactive component in cannabis. Endocannabinoids serve as synaptic circuit breakers and regulate multiple physiological and pathological conditions, e.g. regulation of food intake, immunomodulation, inflammation, analgesia, cancer, addictive behavior, epilepsy and others. This review will focus on uncovering the roles of anandamide and 2-arachidonoylglycerol, the two best characterized endocannabinoids identified to date, in controlling nociceptive responding. The roles of anandamide and 2-arachidonoylglycerol, released under physiological conditions, in modulating nociceptive responding at different levels of the neuraxis will be emphasized in this review. Effects of modulation of endocannabinoid levels through inhibition of endocannabinoid hydrolysis and uptake is also compared with effects of exogenous administration of synthetic endocannabinoids in acute, inflammatory and neuropathic pain models. Finally, the therapeutic potential of the endocannabinoid signaling system is discussed in the context of identifying novel pharmacotherapies for the treatment of pain.

CNS Neurol Disord Drug Targets. 2009 Oct 19;: 19839934 (P,S,G,E,B)
[Cited?]
Cannabinoids and Parkinson's Disease.
Moisés García-Arencibia, Concepción García, Javier Fernández-Ruiz
Departamento de Bioquímica y Biología Molecular and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Facultad de Medicina, Universidad Complutense, 28040-Madrid, Spain. jjfr@med.ucm.es.
Cannabinoid-based medicines have been proposed as clinically promising therapies in Parkinson's disease (PD), given the prominent modulatory function played by the cannabinoid signaling system in the basal ganglia. Supporting this pharmacological potential, the cannabinoid signaling system experiences a biphasic pattern of changes during the progression of PD. Thus, early and presymptomatic stages, characterized by neuronal malfunctioning but little evidence of neuronal death, are associated with desensitization/downregulation of CB1 receptors. It was proposed that these losses may be part of the pathogenesis itself, since they can aggravate different cytotoxic insults which are controlled in part by cannabinoid signals, mainly excitotoxicity but also oxidative stress and glial activation. By contrast, intermediate and, in particular, advanced stages of parkinsonism characterized by a profound nigral degeneration and occurrence of major parkinsonian symptoms (e.g. bradykinesia), are associated with upregulatory responses of CB1 receptors, possibly CB2 receptors too, and the endocannabinoid ligands for both receptor types. This would explain the motor inhibition typical of this disease and the potential proposed for CB1 receptor antagonists in attenuating the bradykinesia typical of PD. In addition, certain cannabinoid agonists have been proposed to serve as neuroprotective molecules in PD, given their well-demonstrated capability to reduce excitotoxicity, calcium influx, glial activation and, in particular, oxidative injury that cooperatively contribute to the degeneration of nigral neurons. However, the potential of cannabinoid-based medicines in PD have been still scarcely studied at the clinical level despite the existence of solid and promising preclinical evidence. Considering the relevance of these preclinical data, the need for finding treatments for motor symptoms that may be alternative to classic dopaminergic replacement therapy, and the lack of efficient neuroprotective strategies in PD, we believe it is of major interest to develop further studies that allow the promising expectations generated for these molecules to progress from the present preclinical evidence towards a real clinical application.
CNS Neurol Disord Drug Targets. 2009 Oct 19;: 19839933 (P,S,G,E,B)
[Cited?]
Cannabinoids and Neurodegenerative Diseases.
J Romero, J Martínez Orgado
Laboratorio de Investigación, Hospital Universitario Fundación Alcorcón and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED). C/ Budapest 1. 28922. Alcorcón, Spain. jromerop@fhalcorcon.es.
Although significant advances have taken place in recent years on our understanding of the molecular mechanisms of different neurodegenerative diseases, its translation into effective therapeutic treatments has not been as successful as could be expected. There is still a dramatic lack of curative treatments for the most frequent disorders and only symptomatic relief for many others. Under this perspective, the search for novel therapeutic approaches is demanding and significant attention and efforts have been directed to studying additional neurotransmission systems including the endocannabinoid system (ECS). The neuroprotective properties of exogenous as well as endogenous cannabinoids have been known for years and the underlying

molecular mechanisms have been recently unveiled. As discussed later, antioxidative, antiglutamatergic and antiinflammatory effects are now recognized as derived from cannabinoid action and are known to be of common interest for many neurodegenerative processes. Thus, these characteristics make cannabinoids attractive candidates for the development of novel therapeutic strategies [1]. The present review will focus on the existing data regarding the possible usefulness of cannabinoid agents for the treatment of relevant neurological pathologies for our society such as Alzheimer's disease, multiple sclerosis, Huntington's disease and amyotrophic lateral sclerosis.
Immunobiology. 2009 Oct 13;: 19833407 (P,S,G,E,B,D)
[Cited?]
Cannabinoid activation of peroxisome proliferator-activated receptors: Potential for modulation of inflammatory disease.
S E O'Sullivan, D A Kendall
School of Graduate Entry Medicine and Health, University of Nottingham, Nottingham, UK.
Cannabinoids act via cell surface G protein-coupled receptors (CB(1) and CB(2)) and the ion channel receptor TRPV1. Evidence has now emerged suggesting that an additional target is the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors. There are three PPAR subtypes alpha, delta (also known as beta) and gamma, which regulate cell differentiation, metabolism and immune function. The major endocannabinoids, anandamide and 2-arachidonoylglycerol, and ajulemic acid, a structural analogue of the phytocannabinoid Delta(9)-tetrahydrocannabinol (THC), have anti-inflammatory properties mediated by PPARgamma. Other cannabinoids which activate PPARgamma include N-arachidonoyl-dopamine, THC, cannabidiol, HU210, WIN55212-2 and CP55940. The endogenous acylethanolamines, oleoylethanolamide and palmitoylethanolamide regulate feeding and body weight, stimulate fat utilization and have neuroprotective effects mediated through PPARalpha. Other endocannabinoids that activate PPARalpha include anandamide, virodhamine and noladin ether. There is, as yet, little direct evidence for interactions of cannabinoids with PPARdelta. There is a convergence of effects of cannabinoids, acting via cell surface and nuclear receptors, on immune cell function which provides promise for the targeted therapy of a variety of immune, particularly neuroinflammatory, diseases.
Recent Pat CNS Drug Discov. 2009 Oct 15;: 19832688 (P,S,G,E,B)
[Cited?]
Pharmacology and Toxicology of Cannabis Derivatives and Endocannabinoid Agonists.
Gilberto Gerra, Amir Zaimovic, Maria L Gerra, Roberto Ciccocioppo, Andrea Cippitelli, Giovanni Serpelloni, Lorenzo Somaini
Health and Human Development Section, United Nations Office on Drugs and Crime, Vienna, Italy. gilberto.gerra@unodc.org.
For centuries Cannabis sativa and cannabis extracts have been used in natural medicine. Delta(9)-tetrahydrocannabinol (THC) is the main active ingredient of Cannabis. THC seems to be responsible for most of the pharmacological and therapeutic actions of cannabis. In a few countries THC extracts (i.e. Sativex(R)) or THC derivatives such as nabilone, and dronabinol are used in the clinic for the treatment of several pathological conditions like chemotherapy-induced nausea and vomiting, multiple sclerosis and glaucoma. On the other hand the severe side effects and the high abuse liability of these agents represent a serious limitation in their medical use. In addition, diversion in the use of these active ingredients for recreational purpose is a concern. Over recent years, alternative approaches using synthetic cannabinoid receptor agonists

or agents acting as activators of the endocannabinoid systems are under scrutiny with the hope to develop more effective and safer clinical applications. Likely, in the near future few of these new molecules will be available for clinical use. The present article review recent study and patents with focus on the cannabinoid system as a target for the treatment of central nervous system disorders with emphasis on agonists.
Neurotherapeutics. 2009 Oct ;6 (4):713-37 19789075 (P,S,G,E,B,D)
[Cited?]
Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside.
Elizabeth J Rahn, Andrea G Hohmann
Neuroscience and Behavior Program, Department of Psychology, University of Georgia, Athens, Georgia 30602.