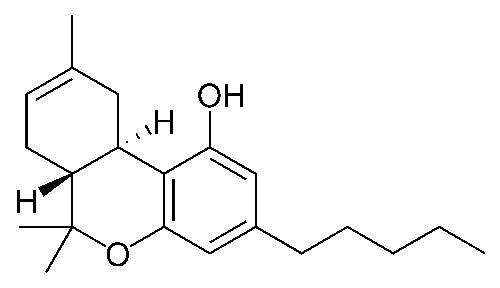
UCL SCHOOL OF PHARMACY

**Cannabinoids: abuse and medical potential**

***Cannabis***

*Cannabis sativa* is the specific name for the marijuana plant, which is grown all around the world and produces the psychoactive cannabinoid **Δ9-tetrahydrocannabinol: Δ9-THC**. The plant synthesises nearly 500 compounds, about 60 of which are cannabinoids, but only in very small amounts. Other than THC, some Cannabis plant varieties also produce high concentrations of **cannabidiol (CBD**), which has little or no psychoactive activity, but has been reported to have some *anxiolytic* properties possibly due to antagonistic effects exerted at cannabinoid receptors. Likewise, another common constituent **Δ9-tetrahydrocannabivarin (THCV)** has been shown to behave as an *antagonist* of some cannabinoid receptors and as an *agonist* at others (see below). A major THC metabolite **cannabinol (CBN)** is also present, but has only weak central activity compared with THC. The characteristic aroma of Cannabis is due to the presence of a mixture of volatile terpinoid compounds *e.g*. *α-humulene.* Some strains of *Cannabis sativa* referred to as **Hemp**, produce very little THC and the stems are therefore used industrially around the world for their fibre content *e.g*. in production of paper, rope, textiles, plastics and in building construction (*hempcrete)*.

The ‘street’ drug is usually found in the form of dried buds and flowers (marijuana), as a resin (hashish, ganja) scraped off the leaves and formed into blocks, or as a concentrated extract known as hashish oil. The earliest documented reference to Cannabis is 2737 BC in China, where it was used to cure rheumatism, malaria, bowel disorders, menstrual cramps and absent-mindedness! The bible book of Exodus in 1450 BC refers to holy anointing oils made from Cannabis, and Ancient Egyptians in 1213 BC used it for glaucoma and inflammation; apparently, Cannabis pollen was found on the mummy of Rameses II. In the 19th century, it was commonly used for the treatment of menstrual cramps and reduction of labour pain, as well as preventing the morning sickness associated with pregnancy, without any apparent harm to the unborn child. In fact, Queen Victoria herself in 1840 regularly used Cannabis medicinally (taken by mouth in the form of an alcoholic tincture) for menstrual pain. <http://medicalmarijuana.procon.org/view.resource.php?resourceID=000143>.



*Cannabis sativa* Δ9-THC

**Cannabis use today:** Recreational Cannabis use first became prevalent in the USA in the 1920’s, but was eventually made illegal in the 1930s. In the early 20th century, the use of Cannabis for its psychoactive effects spread widely in the US, becoming well established among young people by the time of the 1960’s, particularly during the psychedelic “hippie” era, until it was formally classed as a prohibited substance in 1967. This remains the case today, with Cannabis being the most common illicit drug used recreationally for its psychoactive euphoric effects. Common street names for Cannabis include “Marijuana, Weed, Dope, Ganja, Wacky Backy, Hash or Hashish, Grass and Pot”.

More recently, cultivation of subset strains of *Cannabis sativa* (*skunk*) with relatively higher THC content (increasing from the more usual ~5% up to 25% in some strains) and little or no CBD have emerged, with consequently stronger psychoactive effects and thus a more serious possibility of harmful side-effects after prolonged use.

<http://news.bbc.co.uk/1/hi/health/8386344.stm>

Under the Misuse of Drugs Act 1971, Cannabis, up to January 2004 was classified as a class B drug, however it was then transferred from class B to class C, with much (understandable) public support, and less severe penalties for possession and distribution, so that police could nominally concentrate on preventing misuse of more "harder drugs". However, with the increasing use of the stronger *skunk* variety of Cannabis and the accumulating (controversial) evidence that long-term abuse of Cannabis could lead to serious psychiatric problems (schizophrenia), in young people with a family history or pre-disposition towards mental illnesses, this decision was reversed in January 2009, with Cannabis being reclassified as a class B drug, where it remains today.

The usual UK street price of a ‘bag’ of Cannabis is about £5-10 per gram (~£100-£200 per ounce) but quality and price can obviously vary depending on area and dealer. Apparently, the number of illegal Cannabis farms discovered by police in the UK has doubled in the past 4 years. Adulteration of street Cannabis is relatively rare compared with hard drugs like heroin or cocaine, but occasionally, Cannabis is sold laced with other drugs such as PCP, or even glass beads, sand or lead (in Germany, 2008) to increase weight and boost profits! Adulteration with tobacco as a bulking agent is also found.

Since 1970, small amounts (≤ 5 g) of high quality Cannabis containing ~18–19% THC, have been sold freely and legally in the Netherlands for personal use in so-called “licenced coffee shops”; however, a new law recently passed by the Dutch government (2012) will restrict the THC content of Cannabis sold in coffee shops to 15%. Additionally, tourists will be banned from using the cannabis cafes, suggesting that even the liberal Dutch are becoming worried about the increasing recreational use of stronger forms of Cannabis.

*Cannabis legalization by 2 US states:* Colorado and Washington (Nov 2012) voted to legalise the recreational and medicinal use of Cannabis in small amounts by adults (18 years or over). In other US states, the legality varies between “illegal for possession/legal for medicinal use” or “outright illegal”. The Cannabis legalisation debate in the US therefore still continues.

*Cannabis legalization in New York:* On March 31st, 2021, New York became the 16th US state to legalize marijuana for recreational use. Under the new Marijuana Regulation and Taxation Act (MRTA), it is now legal for individuals 21 and older to possess, purchase and transport up to three ounces of marijuana, also up to 24 grams of concentrated cannabis oil. Certain parts of the new law however, will only come into effect at a later date, probably 2023.

People with certain marijuana-related convictions will also have their records expunged immediately. People 21 and older are allowed to use, smoke, ingest or consume cannabis products; they can also give them to others who meet the same age requirement.

Right now, New Yorkers can smoke marijuana almost everywhere they can smoke tobacco but not schools, workplaces or inside a car, in parks, beaches, public transportation, bars and restaurants.

At home, people will be permitted to store (securely) up to five pounds of cannabis. People are legally allowed to smoke cannabis in private residences (with landlord permission), as well as in hotels and motels that permit it. It still remains illegal to drive under the influence of marijuana, as with alcohol.

Eventually, it will be possible to apply for licenses to open storefront cannabis dispensaries, hookah bar-style consumption lounges, bakeries, restaurants, yoga studios, hotels, and wellness centres. Also licenses for the creation of cannabis home delivery businesses.

Patients will no longer be restricted from smoking medical marijuana, and the current 30-day cap on supply for patients will also be doubled. Also under the MRTA, New Yorkers (21 and over) will eventually be able to grow up to three mature plants and three immature plants at their home.

*Cannabis in Italy:* On 25th May 2024, the Italian Government presented an amendment to Italian draft safety bill aiming at prohibiting the cultivation and sale of cannabis even with THC content <2%, for uses other than the allowed industrial and medical ones. Large-scale cultivation + sale however, remains illegal since 1990’s legislation.

In some cities, “cannabis shops” are currently allowed to sell low-strength “legal weed” (cannabis *light)*, essentially hemp-based products containing mainly CBD and <0.6% THC, but even this is controversial, with some politicians aiming to close down the legal weed shops claiming it encourages drug use among young people.

Possession of small quantities of cannabis for recreational use or smoking cannabis in public is still considered an offence and policed by confiscation/formal warnings. Selling any quantity is still a criminal offence punished with 2-6 years in prison/€75K fine.

Since 2007, medicinal cannabis/cannabis products can be legally prescribed by doctors and are available on non-repeat prescription in any pharmacy (officially grown FM2 cannabis flower-heads). Side effects of medicinal cannabis include: tachycardia, hypotension, paranoia, dizziness, memory disturbance, psychiatric disorders, respiratory tract damage, and risk of addiction.

*Cannabis in Germany:* Cannabis in Germany is legal for certain limited medical uses. The personal possession and cultivation of cannabis will become legal for recreational usage by adults (≥ 18 years old) in Germany in a limited capacity beginning on 1 April 2024, as well as adult consumption; however, stricter regulation rules will make it difficult to buy the drug.

From 1 April 2024, it will be legal for German adults to possess up to 25 grams of cannabis in public, up to 50 grams of dried cannabis in private and have up to three cannabis plants at home. Criminal offences will apply to possession beyond these limits. Adult only non-profit cannabis social clubs are due to be legalised in Germany on 1 July 2024. However, legal licensed sales (i.e. sales of cannabis in stores/pharmacies or online and cannabis businesses) will not be allowed. The exclusion zone for cannabis consumption near daycare centres, playgrounds, and schools will be reduced from 200 to 100 metres.

**Routes of administration of Cannabis:** Cannabis is usually smoked or eaten (less effective) in the form of a cake or biscuit. When smoked in the form of a hand-rolled cigarette, usually together with tobacco (“joint, reefer”), the effects are rapid in onset (2-3 minutes) with THC entering the circulation almost immediately (effects lasting 1-3 hours). When taken orally the time to peak is slower, around 1-3 hrs, with a similar duration of action. Cannabis smoke can also be inhaled using a pipe or “bong” (smaller portable version of a *hookah* pipe), where the smoke is first drawn through water to cool it down, and presumably make it less irritant to the throat and lungs.

**How do cannabinoids produce their effects?**

**Cannabinoid receptors**

There are over 400 constituent compounds in marijuana; >60 of these are cannabinoids. The most psychoactive is delta-9-tetrahydrocannabinol (Δ9-THC), which acts on specific brain cannabinoid receptors (CB1), expressed particularly in cerebral cortex (limbic), amygdala, hippocampus [as well as the VTA and nucleus accumbens], cerebellum, basal ganglia (substantia nigra, striatum, globus pallidus), hypothalamus and spinal cord to alter neuronal excitability and neurotransmitter release. CB1 receptors are also found in the liver and adipose tissue, where they activate lipogenesis, the GI tract, urinary and reproductive system and the lung. CB2 receptors on the other hand, which share about 48% amino acid sequence similarity to CB1 receptors and are not involved in the psychoactive effects of Cannabis, are expressed mainly on cells of the immune system (*e.g.* monocytes, macrophages, B- and T- lymphocyte cells), on microglial cells (not neurones), skin keratinocytes, and throughout the GI tract.

Both CB1 and CB2 receptors belong to the G-protein superfamily, and are linked to adenylate cyclase through inhibitory Gi/Goα subunits. CB1 receptors are in fact one of the most abundant G-protein-coupled receptors in the brain, but their coupling efficiency is relatively low, compared for example, with opiate receptors. CB2 receptors are also known to be linked positively to the complex MAPK-ERK (mitogen-activated protein kinase-extracellular signal-regulated kinase) transduction pathway [involved in cell growth, differentiation and migration, as well as in synaptic plasticity] and protein kinases A and C.

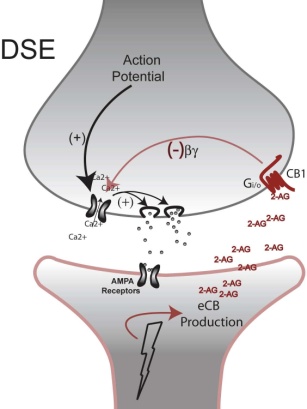
Recent studies have also demonstrated that functional CB1 receptors also exist *intracellularly* associated with acid-filled endosomal and lysosomal compartments.Activation of these receptors with intracellular CB1R ligands increases intracellular calcium concentration in a nicotinic acid-adenine dinucleotide phosphate (NADPH) or inositol 1,4,5-trisphosphate (IP3)-dependent manner. Another subpopulation of CB1Rs is suggested to be present in mitochondria, involved in cellular respiration.

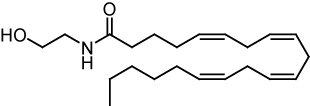
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**Endogenous cannabinoids**

Rather like the endogenous brain opiate-like peptides (enkephalins, endorphins), the brain manufactures several lipophilic *endogenous cannabinoid* ligands (eicosanoids from arachidonic acid) termed **endocannabinoids,** with properties similar to Δ9-THC – mainly **anandamide**, **2-arachidonylglycerol (2-AG)**, and **2-arachidonyl glyceryl ether** (noladin ether), which can bind to synaptic and non-synaptic cannabinoid receptors, and are believed to be involved in the processes of appetite control, mood, pain-sensation and memory formation. A high affinity endocannabinoid transporter is also present. The synthesis of the anandamade occurs thorough *Ca2+-dependent N-acyltransferase* and *N-acylphosphatidylethanolamine-hydrolyzing phospholipase D*, while that of 2-AG is believed to involve *diacylglycerol lipase* and *phospholipase C-β.* Degradation of endocannabinoids to inactive breakdown products, controlled by the enzymes *fatty acid amide hydrolase* (*FAAH)* and *monoacylglycerol lipase* *(MAGL)* respectively. Anandamade interacts with higher affinity with the CB1 receptor, whereas 2-AG prefers to bind to the CB2 receptor.

Activation of central CB1 receptors either by Δ9-THC or endocannabinoids is known to *inhibit* neurotransmitter release and neurotransmission via a *presynaptic* mechanism. So-called *depolarization-induced suppression of inhibition (DSI)*, a strong depolarization of a postsynaptic neurone triggers the production and release of endocannabionoids from the neuronal membrane that diffuse retrogradely to nearby inhibitory presynaptic terminals on adjacent neurones and transiently inhibit GABA release. Likewise, a similar retrograde phenomenon occurs for glutamate release from excitatory nerve terminals (*depolarization-induced suppression of excitation; DSE*). This way, the activity-dependent (non-vesicular) production of endocannabinoids from neuronal cell membranes on demand can exert a fine feedback control on synaptic release and therefore neuronal network activity. The trigger for this cleavage and release of active endocannabinoids from membrane-bound endocannabinoid lipid precursors appears to be a postsynaptic increase of cytosolic free Ca2+ concentration, as can occur during repetitive bursts of intense firing activity (>30 Hz; *e.g.* during slow-wave sleep). The main mechanism of presynaptic inhibition of transmitter release is believed to be via CB1-mediated *inhibition* of terminal N- and P/Q-type Ca2+ channels, although activation of K+ (G-protein coupled inwardly rectifying K+ (GIRK)) channels or direct inhibition of vesicular transmitter release could also be involved. The involvement of presynaptic CB1 receptors is confirmed experimentally by the use of specific CB1 receptor antagonists like *rimonabant* (see below).





Anandamide

**Anandamide** and another endocannabinoid **N-arachidonoyl dopamine**, can also bind to TRPV1 receptors (*transient receptor potential cation channel subfamily V member 1*; also known as the capsaicin receptor or the vanilloid receptor 1), found mainly on peripheral nociceptive neurones (and also in the CNS), which are involved in heat and pain sensation (nociception). The so-called ‘orphan’ receptor GPR55 has also been identified as a potential binding site for cannabinoids.

It is not yet entirely clear how cannabinoid receptor occupation leads to the complex behavioural effects observed, although regulation of dopamine neurones in the mesolimbic reward system is thought to be involved [see Lecture on pleasure/reward pathways].

**The main short-term effects of smoking Cannabis** very much depend on the ‘state of mind’ of the individual and include: mood elevation (euphoria, ‘high’), relaxation, creative thinking, heightened senses, pain relief, reduced nausea, increased appetite (“the munchies”), tachycardia, vasodilation, bronchodilation, dry mouth, hypothermia and short-term memory loss.

**Chronic use** **of Cannabis** may lead to cognitive impairment, agitation, anxiety, paranoia, schizophrenia-like psychosis, delusions, disorientation, or auditory/visual hallucinations, depression, apathy and even possible suicide. Cannabis smoke also contains bronchial irritants, tars and carcinogens in greater concentrations than in tobacco, therefore chronic cannabis smoking can cause bronchitis, emphysema and lung cancer. It is claimed that the lung damage caused by smoking 3-4 Cannabis cigarettes a day is equivalent to smoking 20 tobacco cigarettes. Smoking cannabis can also lead to decreased fertility (reduced plasma testosterone and sperm production, impaired ovulation). There is some evidence that excessive cannabis use during adolescence, at a time when the brain is not completely developed, may have deleterious effects on neural development and later cognitive functioning.

***Cannabis use disorder*** (cannabis addiction) is the continued use of cannabis that can develop in ~10% of users, despite clinically significant distress or impairment which includes:

* a strong desire to take cannabis
* difficulties in controlling its use
* persisting in its use despite clinically harmful consequences
* a higher priority given to cannabis use than to other activities and obligations
* increased tolerance
* sometimes, a mild withdrawal state characterised by anxiety, irritability, depression, restlessness, disturbed sleep, gastrointestinal symptoms, and decreased appetite – symptoms mostly resolve after a few weeks.

By comparison to other drugs, Δ9-THC is not very toxic, therefore no cases of lethal overdose from smoking Cannabis have been reported. Studies in rats indicated that at least up to three months of chronic exposure to Δ9-THC or Cannabis extracts was required to produce neurotoxic effects, equivalent to about seven to ten years daily exposure in humans. Nevertheless, there is still a strong school of thought that believes that Cannabis abuse may be a ‘gateway’ or ‘stepping stone’ to harder drugs such as heroin and cocaine for a small group of “troubled youths”. An extensive study in Amsterdam in 1997 concluded that most (75%) of Cannabis users did not report other drug use.

***Cannabinoid hyperemesis syndrome***

Cannabinoid hyperemesis syndrome (CHS) is a rare condition that causes repeated and severe bouts of vomiting and abdominal pain in some daily long-term users of marijuana. Apart from CNS effects, Δ9-THC can also affect the digestive tract, delaying stomach emptying. It also affects the oesophageal sphincter. Curiously, affected people take a lot of long hot showers during the day to ease their nausea (possible hot temperature effect on the hypothalamus, controlling temperature regulation and vomiting). Symptoms subside within 1-2 days after stopping cannabis use.

**Medicinal use of Cannabis and cannabinoids:**

Medicinal use of herbal Cannabis is still controversial. However, oral Δ9-THC and several synthetic analogues (*e.g*. **nabilone**, and **dronabinol [USA]**) are effective in the relief of:-

* Chemotherapy-induced nausea and vomiting, resistant to conventional anti-emetics.
* Appetite stimulation in cases of severe weight loss in anorexia or patients with AIDS.
* Treatment of acute and chronic pain.

**Nabilone** is available as a 1 mg capsule taken twice daily, increasing to 2 mg twice daily if necessary. It is not recommended for children under the age of 18 years. **Dronabinol** can be prepared in the form of oil-based drops containing 2.5% dronabinol with an oral dose of 1-2 drops, delivering ~2.5 mg per drop, increasing by 1 drop every 1-2 days if necessary. It can also be prepared as a 2.5% alcoholic solution that can be used for inhalation via a vaporization system, or in the form of capsules containing 2.5, 5 or 10 mg active drug.

Cannabis and individual cannabinoids may also be useful in treating–

* Pain symptoms of fibromyalgia (chronic widespread pain),
* MS and spinal cord injury, including spasticity and pain.
* Bladder dysfunction in MS
* Menstrual cramps, morning sickness and labour pain.
* Raised intraocular pressure in late-stage glaucoma.
* Asthma, by inducing bronchodilation.
* Drug-resistant epilepsy; (Cannabidiol: CBD) - *Epidiolex*; now approved by FDA for severe childhood epilepsy: Lennox-Gastaut and Dravet syndromes
* Anxiety (CBD – probably acting as a 5-HT1A agonist).
* Breast, prostate and colorectal cancer.
* Alcohol and opiate addiction.
* Tics in Tourette Syndrome
* L-Dopa-induced dyskinesia in Parkinson’s disease.
* Alzheimer’s and Huntington’s Diseases.

In Jan 2010, an extract of Cannabis - **Nabixmols** (*Sativex;* GW Pharmaceuticals) containing a 1:1 mixture of Δ9-THC and CBD administered as a sublingual spray, was licenced in the UK for the adjunctive symptomatic treatment of MS, neuropathic and cancer related pain. A single metered dose delivers 2.7 mg THC and 2.5 mg CBD. However, NICE do not consider this to be cost-effective and do not recommend its use for MS treatment (£375 for 270 dose spray) (October 2014).

In April 2017 cannabis oil containing CBD was prescribed on the NHS for the first time in the UK for an 11 year old boy suffering from epilepsy. The boy had already been using it, obtained legally in the US to suppress his seizures, but had run out. Under MHRA guidelines doctors are allowed to prescribe CBD for medical purposes. The MHRA (Medicines and Healthcare Products Regulation Agency) says that cannabidiol has a ‘restoring, correcting or modifying’ effect on ‘physiological functions’.

In May 2017, a clinical trial in 120 children and young adults with Dravet syndrome (a complex childhood epilepsy disorder associated with drug-resistant seizures) treated with CBD oral solution (100 mg/ml) for 14 weeks, was published (*The New England J. of Medicine 376, 2011-20*). They found that CBD significantly reduced seizure frequency relative to placebo but was associated with higher rates of adverse events: e.g. diarrhoea, vomiting, fatigue, pyrexia, somnolescence and abnormal liver-function tests. Further studies ae needed to evaluate long-term efficacy and safety.

In June 2018, ***Epidyolex*** (CBD 100 mg/ml oral solution) was approved by the FDA for the treatment of two severe forms of childhood epilepsy: Lennox-Gastaut syndrome and Dravet syndrome in patients two years of age and older.

After changes recently introduced by the Home Secretary, medicinal cannabis oil (cannabidiol: CBD) has now become available for therapeutic use on prescription in the UK from Nov 1st 2018.

“Herbal CBD (hemp oil)” is already available from Health Stores as a “food supplement” (<0.05% THC). These preparations have variable quality and doubtful health benefits.

Prescribable cannabis oil containing CBD is more concentrated allowing for stronger medicinal properties; available only via a specialist hospital doctor for treating drug-resistant nausea/vomiting (cancer chemotherapy), intractable epilepsy (Lennox-Gastaut and Dravet syndromes), and chronic pain/spasticity in MS sufferers.

**Dependence, Tolerance and Withdrawal**

Although some mild *psychological dependence* to Cannabis may develop on prolonged use, [meaning that using Cannabis assumes more importance than other activities in their life, and that they develop a craving for the drug and find it very difficult to stop using it], there is *no physical dependence syndrome*, and *withdrawal effects* are mild (compared with heroin and alcohol withdrawal syndromes), including craving, nausea, sweating and increased restlessness, irritability, mood changes, anger, depression, loss of appetite and insomnia that may last for a week or two after stopping use.

Cannabis therefore has a low addiction potential and is in fact considered less addictive than caffeine! It is claimed that about 10% of users become addicted to Cannabis, but this number increases in those starting young (~17%) and among those using daily (25-50%). Some clinicians believe that adolescents face a greater risk of developing Cannabis dependency as they are at a vulnerable age when the brain is still developing, thus could face later problems with cognitive function and other possible mental disorders such as schizophrenia. Some mild Cannabis *tolerance* can also develop with prolonged, regular use, most likely at the cannabinoid receptor level (downregulation, desensitization, uncoupling), although this is controversial.

**Treatment**

Treatment strategies for Cannabis dependence are relatively limited compared with those available for opiate, alcohol or nicotine dependence, and mainly include psychotherapy (*e.g.* cognitive behavioural therapy (CBT) and motivational enhancement therapy (MET)), social peer support groups, individual counselling and family intervention sessions, to try to encourage the user to adopt a drug-free lifestyle. Pharmacological treatments are also an option - although these have not become firmly established. Various drugs and combinations have been tried with variable success in producing abstinence and reducing Cannabis use and withdrawal in Cannabis addicts:**-**

**Buproprion** (*Zyban*, used for smoking cessation), **naltrexone** (opiate antagonist), **sodium valproate** (antiepileptic and mood stabilizer) (divalproex, *Depakote*) and even small doses of **Δ9-THC** or **dronabinol** (*Marinol*, synthetic cannabinoid**)** combined with **lofexidine** (*BritLofex*: α2-adrenergic receptor agonist-used for opiate dependence). The CB1 cannabinoid receptor antagonist **rimonabant** (*Acomplia:-*originally introduced for the treatment of obesity and smoking cessation), was also found effective in blocking the acute central effects of smoked Cannabis, but this drug has now been withdrawn from use due to serious side-effects (see below). A recent animal study (August 2012) reported that vulnerability to Cannabis addiction may be greater in females than in males, suggesting that withdrawal craving and likelihood to re-use cannabis after abstinence in human addicts may differ between the sexes and thus require distinct prevention strategies and treatments.

**The physiological importance of the endocannabinoid system**

Prior to the discovery of cannabinoid receptors in 1988, it was though, that because of their high lipid solubility, cannabinoids exerted their central effects by dissolving in neuronal cell membrane, and thereby ‘perturbing’ the membrane fluidity and therefore the behaviour of ion channels involved in excitability, rather like the hypothesis originally advocated for the mechanism of action of general anaesthetics. This theory clearly became untenable when (i) specific brain cannabinoid binding sites were demonstrated (ii) when cannabinoids were shown to have a remarkable degree of chemical selectivity and stereoselectivity and (iii) when it was became obvious that all cannabinoids were lipid soluble, but not all possessed psychotropic activity. The discovery of endocannabinoids in 1992 also put a final nail in the coffin of the membrane lipid hypothesis. It is now becoming increasingly apparent that the endocannabinoid system is important in regulating virtually all body systems (nervous, cardiovascular, digestive, endocrine, excretory, immune, musculoskeletal, reproductive), particularly the emotional responses to stress, appetite control and energy regulation and that interference with this system could drastically affect the health of an individual.

**The story of Rimonabant**

**Rimonabant** (*Acomplia*; SR141716) was the first competitive CB1 receptor antagonist introduced clinically in 2006 by Sanofi-Aventis as an anti-obesity drug, to assist along with diet and exercise in weight reduction programmes. It was also effective in treating smoking addicts and to reduce craving in other forms of drug addiction (opiates, alcohol). Although patients treated with the drug showed a significant weight loss and improvement in their lipid levels, some serious adverse effects were soon reported, particularly- enhanced anxiety, higher rates of severe depression and suicidal behaviour and even a *worsening* of the symptoms of MS, such that it had to be withdrawn from the market in 2009. These findings further highlighted the importance of a correct endocannabinoid system ‘tone’ in the body in order to maintain well-being. It has recently been suggested that rare variants of the CB1 receptor gene could pre-dispose some individuals towards development of anxiety and depression.

Since these fundamental discoveries, research into cannabinoid chemisty, function, mechanism of action and possible therapeutic significance has expanded dramatically. Likewise, research into the functions of the endocannabinoid system has also mushroomed. Pubmed searches on: [*cannabinoid NOT endocannabinoid*] yielded 12,410 papers while [*endocannabinoid*] alone gave 5762 papers [November 2013].

**Cannabinoid agonists and antagonists**

A wide range of synthetic cannabinoid receptor specific agonists and antagonists are now available for use in cannabinoid research. These include:-.

***Direct-acting CB1 agonists:*** WIN 55212-2, CP55940, AM2389, AM4054, ACEA, ACPA

***CB1 antagonists:*** SR141716 (*Rimonabant)*, AM251,

***Selective CB2 agonists:*** AM1241, JWH133, JWH015, BML190, HU308, CB65

***CB2 antagonists:*** AM630, SR144528, JTE907

***Non-selective CB agonist:*** HU210

**Transport and enzyme synthesis inhibitors:** [to enhance endocannabinoid signalling]:

***Inhibitor of FAAH*** (the enzyme responsible for the degradation of anandamide) – AM1172

***Inhibitors of anandamide uptake:*** OMDM-2, VDM-11

***Inhibitor of MGL:*** (2-AG-hydrolyzing enzyme monoacylglycerol lipase):JZL184

***Cannabinoid receptor knockout mice:*** CB1 and CB2 receptor knockout mice have also been developed, and are particularly useful when looking for *non-cannabinoid receptor* mediated effects of some cannabinoids. CB1 KO mice are also being used as a genetic model of depression. Double CB1/CB2 receptor KO mice are also useful for studying the possible role of the endocannabinoid system in various pathological processes.

**What’s new in cannabinoid research?**

Several highly interesting and therapeutically promising reports in cannabinoid research have appeared in recent years:-

* ***Cannabinoids and skin****:* Cannabinoids have been found to inhibit human skin keratinocyte proliferation through a non-CB1/CB2 receptor mechanism and have been suggested to have potential therapeutic value in the treatment of psoriasis.
* ***Cannabinoids and diabetes:*** The endocannabinoids and certain plant-derived non-psychoactive cannabinoids such as **cannabidiol (CBD)** and **Δ9-tetrahydrocannabivarin (THCV)**, which have been found to possess potent anti-inflammatory and antioxidant properties may be useful to protect cells from oxidative injury in the treatment of diabetes and diabetic complications such as cardiovascular dysfunction, nephropathy, retinopathy, and neuropathy.
* ***Cannabinoids and Parkinson’s disease:*** CB1 receptor agonists WIN 55212-2 and HU210 have been found to be neuroprotective against damage caused to nigrostriatal dopamine neurones in an animal model of Parkinson’s disease. This implies that the endogenous endocannabinoid system may exert a natural protective role against developing the disease in humans, although there is some experimental evidence to the contrary.
* ***Cannabinoids and Alzheimer’s disease:*** Microglial activation is also a characteristic feature of Alzheimer's disease (AD), and it has been found that the cannabinoids CBD and WIN 55212-2 were neuroprotective against the microglial activation and inflammatory cytokine expression produced by injected β-amyloid (Aβ) in amouse model of AD. Thus, the modulation (enhancement) of the endogenous endocannabinoid system ‘tone’ may present a novel approach for the treatment of AD in humans.
* ***Cannabinoids and stroke:*** It has been shown in a mouse model of ischaemic stroke that the CB2 agonist JWH 133, by inhibiting neutrophil recruitment to the brain, might protect against ischemic brain injury in stroke.
* ***Cannabinoids and GABAA receptors:*** It was recently found that the endocannabinoid 2-AG can directly *potentiate* the synaptic inhibitory effects of low concentrations of GABA by interacting with modulatory binding sites on β2 or γ-subunit-containing GABAA receptors, present *extra*synaptically. This finding could be relevant in the regulation of locomotion and sedation.
* ***Cannabinoids and glycine receptors:*** It has also beenshown that the cannabinoid CBD directly potentiates glycine currents in spinal cord neurones by interacting allosterically at α3-subunit type glycine receptors (α3-GlyRs), suggesting that the therapeutic analgesic value of Cannabis and cannabinoids for the treatment of chronic neuropathic pain and other disease states could be exerted directly by modulating GlyRs [and not via CB1/CB2 receptors].
* ***Cannabinoids and obesity:*** Obesity is associated with insulin resistance and chronic inflammation in insulin-sensitive tissues *e.g.* liver, adipose tissue, kidney, skeletal muscle, pancreatic β–cells. Peripheral CB1Rs may participate in this peripheral metabolic inflammation process thus, 2nd/3rd generation **peripherally-restricted CB1R antagonists** have been developed and tested for treating obesity-related metabolic inflammation without CNS neuropsychiatric side effects. Interestingly, activation of peripheral CB2Rs has anti-obesity effects by decreasing food intake and body weight. Thus, hybrid CB1R antagonist/CB2 agonist compounds have also been developed and tested as anti-obesity agents. Examples:
* **Peripherally-restricted CB1R antagonists:**

AM6545, JD5037, LH-21, AJ5018,AJ5012

**Hybrid CB1R antagonists/CB2R agonists:** GW405833, URB447, AM1710

Han JH, Kim W. (2021). Peripheral CB1R as a modulator of metabolic inflammation. FASEB J. 35(4):e21232.

* ***Endocannabinoids and Covid-19:*** Current treatments for the SARS-Cov-2 virus causing the Covid-19 pandemic include antivirals, corticosteroids, immunoglobulins, antimalarials, interleukin-6 inhibitors, anti-GM-CSF, immunotherapy, antibiotics, oxygen therapy, and circulation support, with limited results and consequent high mortality rate. Other therapeutic approaches thus need to be considered. Since the endocannabinoid system is found in multiple systems within the human body, including the immune system, its activation is being considered as potentially beneficial in decreasing viral entry, viral replication, and proinflammatory cytokines e.g. IL-6, or TNF-a, thus reducing pulmonary inflammation, and the ‘cytokine storm’. Research in this field is urgently needed for a better understanding of the possible impact of endocannabinoid upregulation in this situation.

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* ***CBD and Covid -19:*** Some recent evidence suggests that high-cannabidiol (CBD) –containing cannabis extracts may exert anti-COVID-19 properties at least *in vitro* by down-regulating the expression of ACE2, the functional receptor on cell surfaces through which SARS-CoV-2 enters host cells.

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