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# Cannabis and cannabinoid receptors

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**Abstract**

Cannabis and cannabinoids exert many of their biological functions through receptor-mediated mechanisms. Two types of cannabinoid receptors have been identified, namely $CB_1$ and $CB_2$, both coupled to a G protein. $CB_1$ receptors have been detected in the central nervous system (where they are responsible for the characteristic effects of Cannabis, including catalepsy, depression of motor activity, analgesia and feelings of relaxation and well being) and in peripheral neurons (where their activation produces a suppression in neurotransmitter release in the heart, bladder, intestine and vas deferens). Cannabinoid $CB_2$ receptors have only been detected outside the central nervous system, mostly in cells of the immune system, presumably mediating cannabinoid-induced immunosuppression and antinflammatory effects. With the discovery of cannabinoid receptors for exogenous cannabinoids, also endogenous cannabinoids (anandamide, 2-arachidonylglycerol) have been described. 

*Keywords:* Cannabis; Marijuana; Cannabinoid receptors; Anandamide; 2-Arachidonylglycerol

## 1. Botanical and chemical constituents

Cannabis (Indian hemp) consists of the aerial parts of *Cannabis sativa* L. (Cannabidaceae). The plant is an annual herb indigenous to central and western Asia. It grows as both male and female plants and is cultivated in other tropical and temperate regions for the fibre (production of ropes, carpets, etc.) and seeds,

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which yield 30–35% of a fixed oil (industrial uses). More than 60 cannabinoids have been identified in Cannabis. The most abundant compound is $\Delta^9$-THC, other constituents include cannabinol, cannabidiol, cannabigerol, cannabichromene and the relative acids [1].

Cannabis is mentioned in early Hindu and Chinese works on medicine and its use slowly spread through Persia to the Arabs around the 10th century [2]. It was used by the Mohammedan sect known as the Hashishin or assassins, who came into contact with the Crusaders in the 11th and 12th centuries. The drug probably was introduced into Europe around the time of Napoleon [1]. At the same time, cannabis probably attracted the attention of Americans. *Cannabis sativa* exists in several hundred varieties (races). Three chemical variants have been defined following the cannabinoid content: the 'drug', the 'intermediate' and the 'fibre' type. Both female and male plants produce cannabinoids, but the female plants produce larger amounts of resin. The presence of $\Delta^9$-THC in the aerial parts of the plants (0.1–2.7%) is the reason for the illegal use of Indian hemp as a hallucinogenic drug. There are many different preparations of the crude drugs (marihuana, hashish, charas, ganja, kief, dagga, etc.). The best one, named hashish (4–10% in $\Delta^9$-THC), consists almost exclusively of the glandular hairs and is a brown mass with a conspicuous smell. The most common and efficient method for administering Cannabis is smoking; approximately 20% of the $\Delta^9$-THC content of a cannabis cigarette being absorbed. Oral administration is less efficient and the bioavailability is more variable than when the drug is smoked [1].

## 2. Traditional and modern use of Cannabis and cannabinoids

Medicinal properties of cannabis were recognised some 5000 years ago and potential therapeutic applications that are of either historical or contemporary interest include analgesia, migraine, muscle spasms, seizures, attenuation of nausea and vomiting of cancer chemotherapy, antirheumatic and antipyretic actions, decreased bronchial constriction of asthma and decreased intestinal motility of diarrhoea [3–5]. Some cannabinoid receptor agonists are already used clinically to suppress nausea and vomiting provoked by anticancer drugs (nabilone) or to boost the appetite of AIDS patients ($\Delta^9$-THC) [5]. It is possible that the discovery of subtype cannabinoid receptors will broaden the therapeutic benefice of cannabinoid drugs.

## 3. Cannabinoid receptor pharmacology

Several investigations have shown that many of the known pharmacological effects of cannabinoids are mediated by two type of cannabinoid receptors: these are $CB_1$ receptors, identified in 1988 [6] and subsequently cloned in 1990 [7]; and

$CB_2$ receptors, cloned in 1993 [8]. The two receptors activate similar transduction mechanisms, including inhibition of adenylate cyclase and N-type $Ca^{2+}$-channels.

The $CB_1$ receptor occurs in the brain, where it is responsible for the characteristic effects of cannabis (feelings of relaxation and well-being, increased visual and auditory perception, analgesia, depression of motor activity, catalepsy), and in the peripheral nervous system [9]. In the peripheral nervous system, $CB_1$ receptors are located presynaptically or prejunctionally and their activation can produce a suppression of neurotransmitter release. Stimulation of appetite, vasodilatation (particularly marked on the scleral and conjunctival vessels, producing a typical bloodshot appearance), tachycardia and inhibition of intestinal motility are the main signs of peripheral autonomic stimulation induced by Cannabis [9].

The $CB_2$ receptor so far has only been found outside the central nervous system, mostly in cells of the immune system, presumably mediating cannabinoid-induced immunosuppression, anti-inflammatory and the analgesia associated with inflammatory processes [10].

## 4. Endogenous cannabinoids

As with morphine, the discovery of receptors for exogenous cannabinoids raised the possibility of the existence of endogenous cannabinoids.

The first cannabinoid ligand to be isolated was arachidonyl ethanolamine [6], named anandamide, from 'ananda', the Sanskrit word for 'bliss'. Anandamide can mimic the functional effects of $\Delta^9$-THC, but it is highly susceptible to enzymatic hydrolysis [11]. A synthetic anandamide derivative, methanandamide, which possesses high potency and metabolic stability [12], is often used to investigate the physiological role of endocannabinoids. Other eicosanoid derivatives able to bind to cannabinoid receptors have been isolated from several tissues. Among these, 2-arachidonylglycerol, first isolated from the canine gut and subsequently found in high amounts in the rat brain [13], is considered a true endogenous cannabinoid [10]. In contrast to anandamide, very little pharmacological work on 2-arachidonylglycerol has been done so far.

## 5. Brain cannabinoids in chocolate

A novel group of pharmacological constituents of chocolate, whose main target may be the endogenous cannabinoid system in the brain, has been recently reported [14]. Cocoa powder and chocolate contain three unsaturated *N*-acylethanolamines that could act as cannabinoid mimics either directly (anandamide) or indirectly, by inhibiting anandamide hydrolysis (*N*-oleoylethanolamine and *N*-linoleoylethanolamine). Cannabinoids could cooperate with other pharmacological components of chocolate (methylxanthines, biogenic amines) to produce a chocolate craving in susceptible persons [15].

## 6. Synthetic cannabinoid agonists and antagonists

Cannabinoids agonists are usually classified by chemical structure into four main groups: classical; non-classical; aminoalkylindoles; and eicosanoids (Fig. 1).

The *classical* cannabinoids are dibenzopyrane derivatives and include $\Delta^9$-THC. The second, *non-classical* group consists of a bicyclic and tricyclic analogue of $\Delta^9$-THC that lack a pyran ring. The most used compound of this group is CP 55 940. The third group is given by *aminoalkylindoles*, which are structurally different from members of the first two groups. A well-known agonist of this group is WIN 55 212-2. The *eicosanoids* group contains several arachidonic acid derivatives and the prototypic member of this family is the endogenous ligand anandamide.

The best-established cannabinoid receptors agonists are essentially non-selective. Two compounds, L-759 633 and L-759 656, have more than a 700-fold greater affinity for cannabinoid $CB_2$ than $CB_1$ [16], however, the pharmacological properties of these compounds are still incomplete. Studies from Sanofi Recherche elucidated two cannabinoid antagonists, SR141716A and SR144528 [17,18], which are selective antagonists for the $CB_1$ and $CB_2$ receptors, respectively (Fig. 1). These two compounds are contributing to the deciphering of the endogenous cannabinoid system, both in the nervous system and in the immune response.

## 7. Effects of the $CB_1$ receptor antagonist SR141716A

In several systems SR141716A, administered alone, has effects that are opposite in direction to those produced by cannabinoid receptor agonists (i.e. increases locomotor activity in mice, produces signs of increased arousal in rats, improves social short-term memory in rodents, suppresses appetite in rats, reduces voluntary ethanol intake in ethanol-preferring rats, increases defaecation and intestinal motility in rodents and increases neurotransmitter release from central and peripheral neurones) [5]. The constituted activity of $CB_1$ receptors in these systems, however, could not be attributed unequivocally to the displacement of endocannabinoids as SR141716A behaves as an inverse agonist at the human cannabinoid $CB_1$ receptors [19,20].

## 8. Potential therapeutic applications

Although the detailed biochemistry, physiology and pathophysiology of the endogenous cannabinoid system have not been fully determined, there is already sufficient evidence that a pharmacological modulation of the endogenous cannabinoid system could provide new tools for a number of pathological states. Table 1 shows some potential therapeutic applications of cannabinoid agonists and antago-

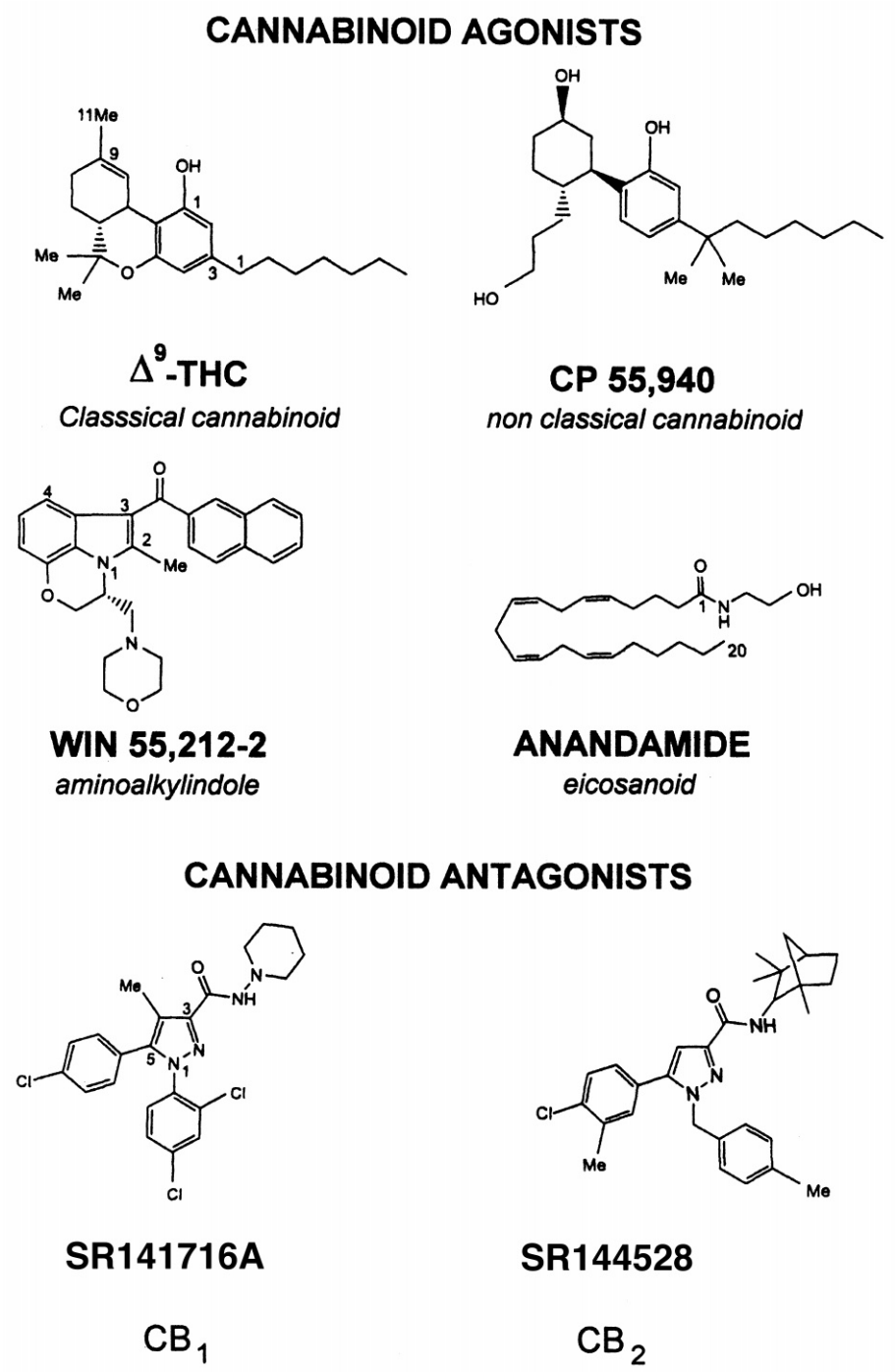


Fig. 1. Chemical structures of cannabinoid ligands.

Table 1
Potential therapeutic applications of cannabinoid drugs

| Drugs | Use |
|---|---|
| $CB_1$ receptor agonists | Treatment of cancer/post-operative pain<br>Anticonvulsivant<br>Antispastic in multiple slerosis or spinal injury |
| Peripheral $CB_1$ receptor agonists | Appetite booster<br>Treatment of gut ipomotility disorders |
| $CB_2$ receptor agonists | Treatment of peripheral 'inflammatory' pain<br>Immunosuppression |
| $CB_1$ receptor antagonists | Treatment of memory deficits<br>Treatment of obesity<br>Treatment of alcohol dependence |
| Peripheral $CB_1$ receptor antagonists | Treatment of gut hypomotility disorders |

nists. Most attention has been given to the therapeutic application of $CB_1/CB_2$ receptor agonists. However, these have the disadvantage that they produce indiscriminate activation of all $CB_1$ or $CB_2$ receptors with a consequent appearance of undesirable side effects. It is likely that drugs, which increase the level of endogenous cannabinoids by inhibiting their metabolism (i.e. anandamide hydrolase inhibitors) or uptake so as to increase their levels at cannabinoid receptors will have a more selective action. Finally, it should be noted that some pharmacological effects of cannabinoids (i.e. antiglaucoma and antiemetic effects) might be not mediated by the cannabinoid receptors. Hence, non-cannabimimetic cannabinoid agonists may be of therapeutic use without causing $\Delta^9$-THC effects.

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