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Mini-review

Cannabinoids and the Endocannabinoid System

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Abstract

The human body possesses specific binding sites on the surface of many cell types for cannabinoids, and our body produces several endocannabinoids, fatty acid derivatives that bind to these cannabinoid receptors (CB) and activate them. CB receptors and endocannabinoids together constitute the endocannabinoid system. Some phytocannabinoids, cannabinoids of the cannabis plant, and a multitude of synthetic cannabinoids produced in the laboratory mimic the effects of endocannabinoids. Δ^9-THC (dronabinol), the pharmacologically most active cannabinoid of the cannabis plant, binds to both types of cannabinoid receptors that have been identified so far, the CB_1 and the CB_2 receptor. These receptors have been found in the central nervous system (brain and spinal cord) and many peripheral tissues and organs. Depending on the kind of cells, on dose and state of the body, activation of CB receptors may cause a multitude of effects including euphoria, anxiety, dry mouth, muscle relaxation, hunger and pain reduction. Besides activation of CB receptors several other approaches are under investigation to influence the cannabinoid system with therapeutic intent, including blockade of CB receptors (antagonism) and modulation of endocannabinoid concentrations by inhibition of their degradation. Currently, several preparations that stimulate cannabinoid receptors (dronabinol, nabilone and cannabis) and one compound that blocks the CB_1 receptor (rimonabant) are used medicinally.

Keywords: Cannabis, THC, cannabinoid, cannabinoid receptor, endocannabinoid, therapeutic use.

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Introduction

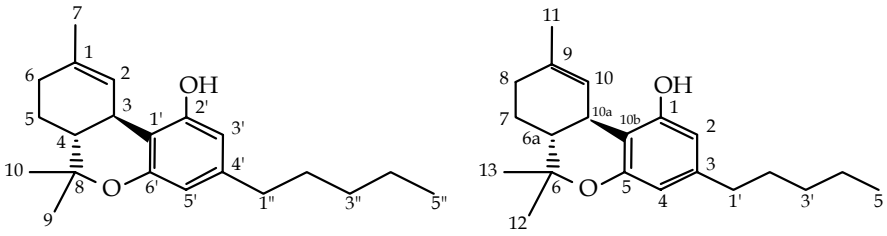
Δ^9-tetrahydrocannabinol (THC) is thought to be the pharmacologically most active cannabinoid of the cannabis plant and its products marijuana (cannabis herb) and hashish (cannabis resin). The majority of THC effects are mediated through agonistic actions at cannabinoid receptors of the human or animal body. Agonistic action means that receptors are activated in contrast to antagonistic action, i.e. blockade of receptor effects.

Cannabinoid receptors and endocannabinoids, compounds produced by the body that bind to these receptors, together constitute the endocannabinoid system. This system is of great importance for the normal function of the body and is millions of years old. It has been found in mammals, birds, amphibians, fish, sea urchins, molluscs and leeches. The mechanism of action of cannabinoids is best investigated for THC and other cannabinoids that bind to known cannabinoid receptors, while the mode of action of other cannabinoids of therapeutic interest, among them cannabidiol (CBD), is less well established.

Extended reviews on the issues presented in this short article are available at [2,4,5,7,9]. Additional and up-to-date information is available from the IACM-Bulletin [8].

Cannabinoids

Cannabinoids were originally regarded as any of a class of typical C21 groups of compounds present in Cannabis sativa L.. The modern definition is termed with more emphasis on synthetic chemistry and on pharmacology, and encompasses kindred structures, or any other compound that affects cannabinoid receptors.



Monoterpenoid numbering Dibenzopyran numbering

Figure 1. Chemical structure of THC (dronabinol), the main cannabinoid in the cannabis plant, according to the monoterpenoid system (Δ^1-THC) and dibenzopyran system (Δ^9-THC).

This has created several chemical sub-categories that take into consideration the various forms of natural and synthetic compounds.

It has been proposed to use the term phytocannabinoid for the natural plant compounds and endocannabinoids for the natural animal compounds, the endogenous ligands of the cannabinoid receptors. Synthetic agonists of these receptors have been classified according to their degree of kinship (e.g. "classical" vs. "non-classical") with phytocannabinoids.

Natural plant cannabinoids are oxygen-containing aromatic hydrocarbons. In contrast to most other drugs, including opiates, cocaine, nicotine and caffeine, they do not contain nitrogen, and hence are not alkaloids. Phytocannabinoids were originally thought to be only present in the cannabis plant (Cannabis sativa L.), but recently some cannabinoid type bibenzyls have also been found in liverwort (Radula perrottetii and Radula marginata).

More than 60 cannabinoids have been detected in cannabis, mainly belonging to one of 10 subclasses or types [3], of whom the cannabigerol type (CBG), the cannabichromene type (CBC), the cannabidiol type (CBD), the Δ^9-THC type, and the cannabinol type (CBN) are the most abundant. Cannabinoid distribution varies between different cannabis strains and usually only three or four cannabinoids are found in one plant in concentrations above 0.1%. Δ^9-THC is largely responsible for the pharmacological effects of cannabis including its psychoactive properties, though other compounds of the cannabis plant also contribute to some of these effects, especially CBD, a non-psychoactive phytocannabinoid common in some cannabis strains that has anti-inflammatory, analgesic, anti-anxiety and anti-psychotic effects.

11-OH-Δ^9-tetrahydrocannabinol (11-OH-THC) is the most important psychotropic metabolite of Δ^9-THC with a similar spectrum of actions and similar kinetic profiles as the parent molecule. 11-nor-9-carboxy-THC (THC-COOH) is the most important non-psychotropic metabolite of Δ^9-THC.

Cannabinoid Receptors

To date two cannabinoid receptors have been identified, the CB_1, and the CB_2 receptor. They differ in signaling mechanisms and tissue distribution. Activation of cannabinoid receptors causes inhibition of adenylat cyclase, thus inhibiting the conversion of ATP to cyclic AMP (cAMP). Other mechanisms have also been observed, e.g. interaction with certain ion channels.

Both CB_1 and CB_2 receptors belong to the large family of the G-protein-coupled receptors (GPCR). GPCRs are the most common receptors, containing 1000-2000 members in vertebrates. Cannabinoid CB_1 receptors are among the most abundant and widely distributed GPCRs in the brain.

Activation of the CB_1 receptor produces effects on circulation and psyche common to cannabis ingestion, while activation of the CB_2 receptor does not. CB_1 receptors are mainly found on nerve cells in the brain, spinal cord and peripheral nervous system, but are also present in certain peripheral organs and tissues, among them endocrine glands, salivary glands, leukocytes, spleen, heart and parts of the reproductive, urinary and gastrointestinal tracts. Many CB_1 receptors are expressed at the terminals of central and peripheral nerves and inhibit the release of other neurotransmitters. Thus, CB_1 receptor activation protects the nervous system from over-activation or over-inhibition by neurotransmitters. CB_1 receptors are highly expressed in regions of the brain, which are responsible for movement (basal ganglia, cerebellum), memory processing (hippocampus, cerebral cortex) and pain modulation (certain parts of the spinal cord, periaqueductal grey), while their expression in the brainstem is low, which may account for the lack of cannabis-related acute fatalities. The brainstem controls, among others, respiration and circulation.

CB_2 receptors occur principally in immune cells, among them leukocytes, spleen and tonsils. One of the functions of CB receptors in the immune system is

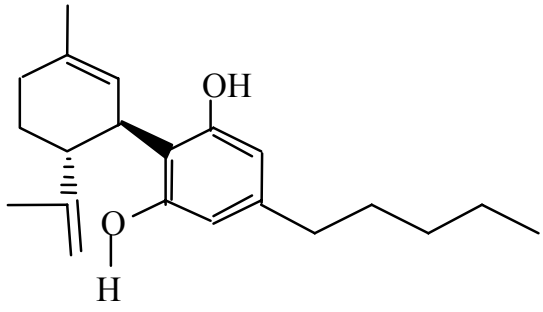


Figure 2. Cannabidiol

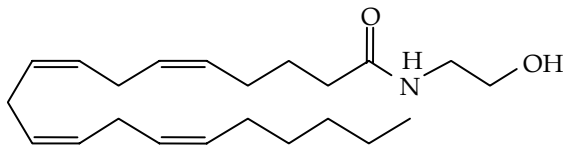


Figure 3. Arachidonoylethanolamide (AEA, anandamide)

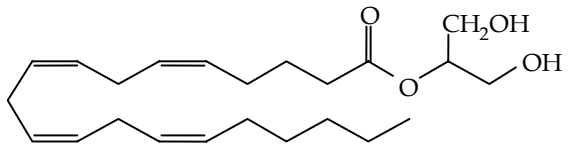


Figure 4. 2-Arachidonoylglycerol (2-AG)

modulation of release of cytokines, which are responsible for inflammation and regulation of the immune system. Since compounds that selectively activate CB_2 receptors (CB_2 receptor agonists) do not cause psychological effects, they have become an increasingly investigated target for therapeutic uses of cannabinoids, among them analgesic, anti-inflammatory and anticancer actions.

There is increasing evidence for the existence of additional cannabinoid receptor subtypes in the brain and periphery. One of these receptors may be the orphan G-protein-coupled receptor GPR55 [1]. Other receptors may be only functionally related to the known cannabinoid receptors than have a similar structure as CB_1 and CB_2.

Endocannabinoids

The identification of cannabinoid receptors was followed by the detection of endogenous ligands for these receptors, named endocannabinoids. In the brain endocannabinoids serve as neuromodulators. All endocannabinoids are derivatives of polyunsaturated fatty acids, thus differing in chemical structure from phytocannabinoids of the cannabis plant. Among the endocannabinoids so far identified are anandamide (N-arachidonoylethanolamide, AEA), 2-arachidonoylglycerol (2-AG), 2-arachidonylglyceryl ether (noladin ether), O-arachidonoyl-ethanolamine (virodhamine), and N-arachidonoyl-dopamine (NADA). Anandamide and NADA do not only bind to cannabinoid receptors but also share the ability of capsaicin, a constituent of hot chilli peppers, to stimulate vanilloid (TRPV1) receptors.

The first two discovered endocannabinoids, anandamide and 2-AG, have been most studied. In contrast to other brain chemical signals they are not produced and stored in the nerve cells but produced "on demand" (only when necessary) from their precursors and then released from cells. After release, they are rapidly deactivated by uptake into cells and metabolized. Metabolism of anandamide and 2-AG occurs mainly by enzymatic hydrolysis by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (2-AG only).

Affinity for the Cannabinoid Receptor

Cannabinoids show different affinity to CB_1 and CB_2 receptors. Synthetic cannabinoids have been developed that act as highly selective agonists or antagonists at one or other of these receptor types. Δ^9-THC has approximately equal affinity for the CB_1 and CB_2 receptor, while anandamide has marginal selectivity for CB_1 receptors. However, the efficacy of THC and anandamide is less at CB_2 than at CB_1 receptors.

Tonic Activity of the Endocannabinoid System

When administered by themselves antagonists at the cannabinoid receptor may behave as inverse agonists in several bioassay systems. This means that they do not only block the effects of endocannabinoids but produce effects that are opposite in direction from those produced by cannabinoid receptor agonists, e.g. cause increased sensitivity to pain or nausea, suggesting that the cannabinoid system is tonically active. This tonic activity may be due a constant release of endocannabinoids or from a portion of cannabinoid receptors that exist in a constitutively active state.

Tonic activity of the cannabinoid system has been demonstrated in several conditions. Endocannabinoid levels have been demonstrated to be increased in a pain circuit of the brain (periaqueductal grey) following painful stimuli. Tonic control of spasticity by the endocannabinoid system has been observed in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice, an animal model of multiple sclerosis. An increase of cannabinoid receptors following nerve damage was demonstrated in a rat model of chronic neuropathic pain and in a mouse model of intestinal inflammation. This may increase the potency of cannabinoid agonists used for the treatment of these conditions. Tonic activity has also been demonstrated with regard to appetite control and with regard to vomiting in emetic circuits of the brain.

Therapeutic Prospects

Mechanisms of action of cannabinoids are complex, not only involving activation of and interaction at the cannabinoid receptor, but also activation of vanilloid receptors, increase of endocannabinoid concentration, antioxidant activity, metabolic interaction with other compounds, and several others. CB receptor antagonists (blockers) are in clinical use for the treatment of obesity and under investigation for the treatment of nicotine and other dependencies.

Aside from phytocannabinoids and cannabis preparations, cannabinoid analogues that do not or only weakly bind to the CB_1 receptor are attractive com-

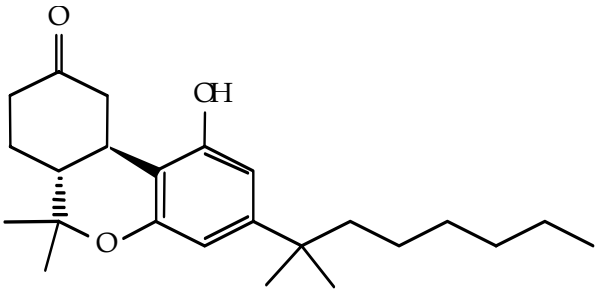


Figure 5. Nabilone

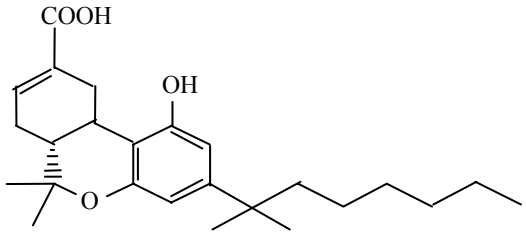


Figure 6. CT3 (ajulemic acid, IP751)

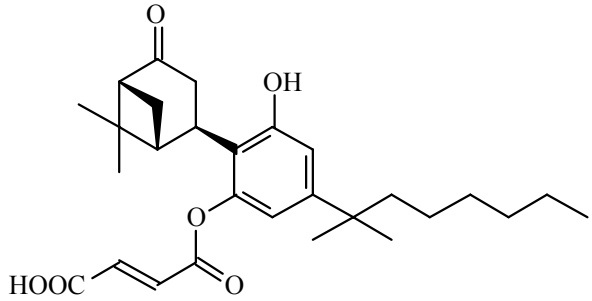


Figure 7. Cannabinor

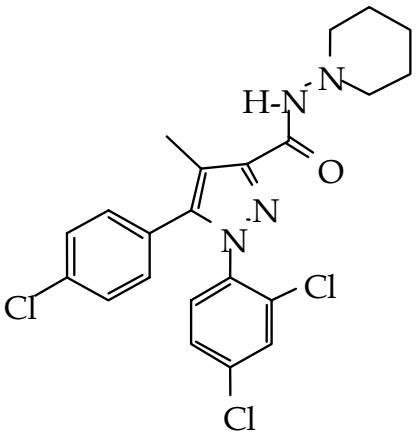


Figure 8. Rimonabant (SR 141716A), Aclompia®

pounds for clinical research. Additional ideas for the separation of the desired therapeutic effects from the psychotropic action comprise the concurrent administration of THC and CBD, the design of CB_1 receptor agonists that do not cross the blood brain barrier, and the development of compounds that influence endocannabinoid levels by inhibition of their membrane transport (transport inhibitors) or hydrolysis (e.g. FAAH inhibitors). For example, blockers of anandamide hydrolysis were able to reduce among others, anxiety, pain, cancer growth, and colitis in animal tests. Drugs that enhance the response of the CB_1 receptor to endogenously released endocannabinoids by binding to the so-called allosteric site on this receptor are also likely to be more selective than compounds that activate this receptor directly [10].

Modulators of the cannabinoid system in clinical use and under investigation

Currently two cannabinoid receptor agonists, dronabinol and nabilone, a cannabis extract (Sativex®), and a cannabinoid receptor antagonist (rimonabant) are in medical use. In addition, cannabis herb produced according to pharmaceutical standards and supervised by the Office of Medicinal Cannabis of the Dutch Health Ministry is available in pharmacies of the Netherlands [4]. In some countries the possession of small amounts of cannabis either for recreational or medicinal use is allowed or tolerated, such as in the Netherlands, Spain, Belgium and some regions of Switzerland. Eleven states of the USA (Alaska, California, Colorado, Hawaii, Maine, Montana, Nevada, Oregon, Rhode Island, Vermont, Washington) have legalized the medical use of cannabis under state law, while it remains illegal under federal law. In Canada it is possible to apply for a certificate of exemption to use otherwise illegal cannabis for medical purposes, and the Health Ministry (Health Canada) sells cannabis herb to these patients if they do not want to grow it themselves.

Dronabinol is the international non-proprietary name (INN) for Δ^9-THC, the main psychoactive compound of cannabis. In 1985 the Food and Drug Administration (FDA) of the United States approved Marinol® Capsules, which contain synthetic dronabinol (2.5 mg, 5 mg or 10 mg), for nausea and vomiting associated with cancer chemotherapy in patients that had failed to respond adequately to conventional anti-emetic treatments. Marinol® is manufactured by Unimed Pharmaceuticals, a subsidiary of Solvay Pharmaceuticals. Marinol® has been on the market in the USA since 1987. In 1992 the FDA approved Marinol® Capsules for the treatment of anorexia associated with weight loss in patients with AIDS. Marinol is also available on prescription in several other countries including Canada and several European countries. In Germany and Austria dronabinol, which is manufactured by the two German companies THC Pharm and Delta 9 Pharma, may be bought by pharmacies to produce dronabinol capsules or solutions.

In 1985 the FDA also approved Cesamet® Capsules for the treatment of nausea and vomiting associated with chemotherapy. Cesamet® made by Eli Lilly and Company contains nabilone, a synthetic derivative of dronabinol. However, it was not marketed in the USA and Lilly discontinued the drug in 1989. Cesamet® is also available in the United Kingdom marketed by

Cambridge Laboratories and in several other European countries. In 2006 nabilone (Cesamet®) again got approval by the FDA as a prescription treatment for nausea and vomiting associated with chemotherapy. It is marketed by Valeant Pharmaceuticals International, which bought the drug from Eli Lilly in 2004 and also sells it in Canada.

In 2005 Sativex® received approval in Canada for the symptomatic relief of neuropathic pain in multiple sclerosis. Sativex® is produced by the British company GW Pharmaceuticals and marketed in Canada by Bayer Health Care. Sativex® is a cannabis extract, which is sprayed in the oromucosal area and contains approximately equal amounts of dronabinol (THC) and cannabidiol (CBD). There is also limited access to Sativex® in the UK and Spain. Sativex is currently under review for approval as a prescription medication for treatment of spasticity in multiple sclerosis in the United Kingdom, Spain, Denmark and the Netherlands.

The cannabinoid receptor antagonist rimonabant received a positive recommendation for approval by the European Medicines Agency in 2006. It is available in the United Kingdom under the trade name Acomplia® for the treatment of obesity. Acomplia® tablets contain 20 mg of rimonabant. The drug is manufactured by Sanofi Aventis.

Preparations under investigation in clinical phase II or III studies include the capsulated cannabis extract Cannador®, which contains dronabinol and other cannabinoids in a ratio of 2 to 1 and is being investigated by the Institute for Clinical Research in Berlin and the pharmaceutical company Weleda, ajulemic acid, a synthetic derivative of THC-COOH, which is also called CT3 or IP751 and is being investigated by Indevus Pharmaceuticals, and cannabinor, a synthetic cannabinoid that binds selectively to the CB_2 receptor and is being investigated by Pharmos Corporation.

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