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Cannabis and Cannabinoids: Pharmacology and Rationale for Clinical Use

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Key Words

Cannabinoid receptors · Anandamide · Tetrahydrocannabinol · Marinol · Nabilone · SR141716A · Multiple sclerosis · Chronic pain · Appetite disorders · Schizophrenia

Summary

It is now known that there are at least two types of cannabinoid receptors. These are CB_1 receptors, present mainly on central and peripheral neurones, and CB_2 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 CB_1 and CB_2 receptor ligands and fuelled renewed interest in the clinical potential of cannabinoids. Two cannabinoid CB_1 receptor agonists are already used clinically, as antiemetics or as appetite stimulants. These are Δ^9-tetrahydrocannabinol (THC) and nabilone. Other possible uses for CB_1 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. CB_1 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 CB_2 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 CB_1 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 CB_1 receptors to produce their sought-after effects.

Schlüsselwörter

Cannabinoid-Rezeptoren · Anandamid · Tetrahydrocannabinol · Marinol · Nabilon · SR141716A · Multiple Sklerose · Chronischer Schmerz · Appetitstörungen · Schizophrenie

Zusammenfassung

Cannabis und Cannabinoide: Pharmakologie und Rationale für die klinische Anwendung

Es ist nun bekannt, dass es wenigstens zwei Typen von Cannabinoid-Rezeptoren gibt. Dies sind die CB_1-Rezeptoren, die vor allem auf zentralen und peripheren Neuronen gefunden werden, sowie die überwiegend auf Immunzellen auftretenden CB_2-Rezeptoren. Endogene Cannabinoid-Rezeptoragonisten («Endocannabinoide») wurden ebenfalls identifiziert. Die Entdeckung dieses «endogenen Cannbinoid-Systems» hat zur Entwicklung selektiver CB_1- und CB_2-Rezeptorliganden geführt und das erneute Interesse am klinischen Potential der Cannabinoide angeheizt. Zwei Cannabinoid-CB_1-Rezeptoragonisten werden bereits klinisch eingesetzt, als Antiemetika und Appetitanreger. Es sind dies Δ^9-Tetrahydrocannabinol (THC) und Nabilon. Weitere mögliche Verwendungsmöglichkeiten von CB_1-Rezeptoragonisten umfassen die Unterdrückung von Muskelspasmen/-spastizität bei Multipler Sklerose oder Rückenmarkserkrankungen, die Linderung chronischer Schmerzen und die Behandlung von Glaukom und Bronchialasthma. CB_1-Rezeptorantagonisten könnten ebenfalls klinisch eingesetzt werden, zum Beispiel zur Unterdrückung des Appetits sowie zur Behandlung von Schizophrenie oder Störungen von Kognition und Gedächtnis. Dies gilt ebenso für CB_2-Rezeptorliganden und Substanzen, die Cannabinoid-Rezeptoren indirekt aktivieren, indem sie die Endocannabinoid-Konzentration an den Cannabinoid-Rezeptoren erhöhen. Bei oraler Aufnahme scheint THC variabel absorbiert zu werden und ein enges «therapeutisches Fenster» zu besitzen (Dosisbreite, in der es effektiv ist, ohne signifikante unerwünschte Wirkungen hervorzurufen). Das erschwert die Voraussage einer Dosis, die sowohl effektiv als auch für den Patienten tolerabel sein wird, und zeigt einen Bedarf für bessere Cannabinoid-Zubereitungen und Formen der Applikation an. Für die vollständige Nutzung des therapeutischen Potentials von Cannabis oder CB_1-Rezeptoragonisten wird es wichtig sein, objektiv und schlüssig festzustellen, (a) ob diese Mittel eine Wirksamkeit gegen bestimmte Symptome besitzen, die von klinischer Relevanz ist, und, wenn das so ist, ob die Vorteile die Risiken überwiegen, (b) ob Cannabis individuellen Cannabinoiden therapeutisch überlegen ist, (c) ob bei Störungen, bei denen Cannabinoide wirksam sind, ein Bedarf für zusätzliche medikamentöse Behandlungsformen besteht und (d), ob es möglich sein wird, Medikamente zu entwickeln, die eine verringerte psychotrope Aktivität aufweisen und ihre Fähigkeit bewahren, zur Erzielung ihrer gewünschten Wirkungen über spezifische CB_1-Rezeptoren zu wirken.

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The plant *Cannabis sativa* is the source of a set of more than 60 oxygen-containing aromatic hydrocarbon compounds called cannabinoids. One of these, Δ^9-tetrahydrocannabinol (Δ^9-THC), is responsible for most of the psychotropic properties of cannabis [1]. It is also of interest because it is one of just two cannabinoids that is licensed for medical use. Thus Δ^9-THC, as the oral preparation dronabinol (Marinol®, Roxane Laboratories Inc., Columbus, OH, USA), is available in the USA for the suppression of nausea and vomiting provoked by anticancer drugs and for the reversal, through appetite stimulation, of body weight loss experienced by AIDS patients. The other cannabinoid that is permissible to use clinically is nabilone (Cesamet™, Cambridge Laboratories, Newcastle upon Tyne, UK), a synthetic analogue of Δ^9-THC that is also given orally. This compound is licensed for use in the UK, again to suppress nausea and vomiting produced by anticancer drugs.

Because psychotropic cannabinoids have high lipid solubility and low water solubility, they were long thought to owe their pharmacological properties to an ability to perturb the phospholipid constituents of biological membranes [1]. However, all this changed with the discovery of specific cannabinoid receptors. These are CB_1 receptors, cloned in 1990, and CB_2 receptors, cloned in 1993 [2]. Both of these receptor types are coupled through $G_{i/o}$ proteins, negatively to adenylate cyclase and positively to mitogen-activated protein kinase. CB_1 receptors are also coupled to ion channels through $G_{i/o}$ proteins, negatively to N-type and P/Q-type calcium channels and positively to A-type and inwardly rectifying potassium channels. Under certain conditions, CB_1 receptors may also activate adenylate cyclase through G_s proteins [3]. Other effector mechanisms have also been proposed [2]. CB_1 receptors are found mainly on neurones in the brain, spinal cord, and peripheral nervous system where they can inhibit neurotransmitter release when activated. They exist in particularly high concentrations in the basal ganglia and in parts of the cerebral cortex and hippocampus. The physiological roles of CB_2 receptors, which occur principally in immune cells, are proving more difficult to establish. However, it seems likely that these receptors modulate immune function in health and/or disease, raising the possibility that cannabinoid receptor ligands may be effective not only in treating symptoms of multiple sclerosis (see below), but also against its underlying causes. The discovery of CB_1 receptors in 1990 was followed by the demonstration, in 1992, that mammalian tissues can produce agonists for these receptors. The most important of these 'endocannabinoids' are arachidonoylethanolamide (anandamide) and 2-arachidonoyl glycerol, both of which are thought to serve as neurotransmitters [1, 2]. Current knowledge about endocannabinoid biosynthesis, release and fate is detailed elsewhere [4, 5]. Cannabinoid CB_1 and CB_2 receptors and endocannabinoids together constitute the 'endocannabinoid system'.

These recent advances in our understanding of cannabinoid pharmacology have prompted the development both of selective CB_1 and CB_2 receptor agonists and antagonists [2, 6] and of drugs that inhibit the tissue uptake or metabolism of endocannabinoids [1, 7]. The most important antagonists to have been developed are the CB_1-selective agent, SR141716A, and the CB_2-selective agent, SR144528 [6]. When administered by themselves, SR141716A and SR144528 produce effects in some biological systems that are opposite in direction to those produced by cannabinoid receptor agonists [2]. These 'inverse cannabimimetic effects' are presumably provoked in biological systems in which the endocannabinoid system is tonically active [7]. Agonists with the greatest selectivity for CB_1 receptors have so far all proved to be anandamide analogues, e. g. methanandamide [1, 8]. Important CB_2-selective agonists include L759633 and L759656 [9]. Of the three cannabinoid receptor agonists that have been most commonly used as pharmacological tools, WIN55212-2, shows some degree of CB_2 selectivity (up to 30-fold) [7], whereas CP55940 and Δ^9-THC bind equally well to CB_1 and CB_2 receptors [7, 8].

The discovery of the endocannabinoid system has been paralleled by a growing interest in the possibility that cannabinoid receptor ligands may have therapeutic applications in addition to those of anti-emesis and appetite stimulation (see above). CB_1 receptor antagonists could prove to be of value as appetite suppressants, in the management of acute schizophrenia and/or for ameliorating cognitive/memory dysfunctions associated with disorders such as Alzheimer's disease [6, 10–12]. CB_1 receptor agonists have several potential therapeutic uses. Among these are the management of glaucoma, bronchial asthma and pain and the suppression of muscle spasticity/spasm associated with conditions such as multiple sclerosis or spinal cord injury [13, 14]. An answer to the question of whether drugs that activate or block CB_2 receptors have therapeutic potential, e. g. as immunomodulators, must await a more complete characterization of this component of the endocannabinoid system. In some instances it may be of therapeutic advantage to administer drugs that activate the endogenous cannabinoid system indirectly by selectively inhibiting the tissue uptake or metabolism of endocannabinoids so as to increase the levels of these compounds at cannabinoid receptors. Such drugs should be more selective than direct cannabinoid receptor agonists as they are unlikely to affect all parts of the endocannabinoid system at one time, producing instead effects only at sites where on-going production of endogenous cannabinoids is taking place. Not all effects of cannabinoids are mediated by receptors, and some of these may also have clinical applications. Of particular importance is evidence from whole animal and tissue experiments that the psychotropically inactive cannabinoid, (+)-11-hydroxy-Δ^8-THC-dimethylheptyl (HU-211, dexanabinol) is effective against neuropathic pain and protects from neurotoxic changes in the brain arising, e. g., from ischaemia [15].

For cannabis and cannabinoid receptor agonists, there is particularly strong evidence to warrant the setting up of clinical trials that will test the efficacy of these agents against the muscle spasticity/spasm and chronic pain of multiple sclerosis and spinal cord injury [13, 14]. This evidence falls essentially into 3 categories: preclinical, clinical and anecdotal.

(a) Preclinical data. There are reports that the synthetic cannabinoid receptor agonist, WIN55212-2, can decrease the severity of dystonia in mutant Syrian hamsters with primary generalized dystonia and that, in rats and guinea pigs, Δ^8- or Δ^9-THC

can delay the onset and reduce the intensity of the signs of experimental autoimmune encephalomyelitis, a putative animal model of multiple sclerosis [16–18]. Other animal experiments have shown that cannabinoid receptor agonists suppress spinal reflexes and that they can produce hypokinesia and catalepsy, changes in motor function that are presumably mediated at least in part by the large populations of cannabinoid CB_1 receptors present in the basal ganglia of the brain [1, 2, 19]. Whether cannabinoids produce their putative antispasticity effect by acting at these brain sites remains to be established. Results from experiments with various animal models of pain also suggest that cannabinoid receptor agonists can act through central and/or peripheral cannabinoid CB_1 receptors to suppress behavioural responses to various kinds of pain, including hyperalgesia and neuropathic pain [20–28].

(b) Clinical data. There have so far been 7 clinical investigations, albeit with rather small numbers of patients [14]. The resulting data suggest that cannabis, Δ^9-THC or nabilone can reduce the intensity of at least some signs and symptoms of multiple sclerosis or spinal cord injury, particularly spasticity, pain, tremor and nocturia [29–35]. There is also clinical evidence that cannabinoids can relieve other types of pain. For example, double-blind, placebo controlled trials have shown oral Δ^9-THC to suppress continuous moderate cancer pain [36, 37] and intramuscular L-nantradol to be effective against acute postoperative pain [38].

(c) Anecdotal data. Among these are the responses to a questionnaire by 112 multiple sclerosis patients who claim to self-medicate with cannabis [39]. Of the patients in this survey with the following symptoms, over 90% reported improvement after taking cannabis: spasticity at sleep onset (96.5%), pain in muscles (95.1%), spasticity when waking at night (93.2%), pain in legs at night (92.3%), tremor of arms/head (90.7%), and depression (90.6%).

Like most drugs, cannabinoids can induce adverse effects [13, 14, 40]. Among these are impairment of cognitive function and memory, including difficulty in concentrating and thinking, reductions in psychomotor coordination and performance, and changes in autonomic, endocrine and reproductive function [40–44]. Cardiovascular changes are also induced, particularly tachycardia, postural hypotension and supine hypertension [40, 45]. As a result, patients with coronary arteriosclerosis or congestive heart failure should not take psychotropic cannabinoids. Associated with these effects of cannabinoids may be dysphoria, anxiety, panic reactions and even psychoses [40, 42, 46]. Consequently, it would be unwise to give psychotropic cannabinoids to patients with schizophrenia (overt or latent). Tolerance to many of the pharmacological effects of cannabinoids can be induced in animals and man [40, 47–49]. However, the extent to which tolerance develops to the sought-after effects of cannabinoids when these are administered at therapeutic dose levels has still to be determined. Withdrawal of cannabis or of psychotropic cannabinoid administration can precipitate abstinence signs in man. However, these signs are both transient and mild and their significance when cannabinoids are used clinically is still unknown [40, 47–49]. The clinical significance of the ability of cannabinoids to retard foetal development and to induce foetal resorption in animals also remains to be established [40]. Because of the tars produced during the combustion process, cannabis smoke may be carcinogenic and can also injure the bronchial mucosa, decrease airway conductance and impair antibacterial activity of alveolar macrophages [40, 50].

In conclusion, there is sufficient evidence to warrant additional clinical studies with cannabis and/or cannabinoid receptor agonists. These should be directed at establishing objectively and conclusively whether cannabinoids do indeed have efficacy against selected symptoms that is of clinical significance and, if they do, whether the benefits outweigh the risks. There is also a need to establish whether mixtures of cannabinoids have any therapeutic advantages over individual cannabinoids, there being some evidence that, in addition to Δ^9-THC, other constituents of cannabis contribute to its putative beneficial effects either directly or indirectly [15]. Another important need is for strategies that will selectively reduce the psychotropic effects of cannabinoids [15]. Also required is further basic research directed at characterizing the pharmacology and physiology of both CB_1 and CB_2 components of the endocannabinoid system more fully. This in turn may reveal additional therapeutic applications for cannabinoids. The question of whether there are other cannabinoid receptor types/subtypes also needs to be addressed [51]. Last but not least, there seems to be a need for additional formulations and modes of administration for cannabinoids. Thus, when taken orally, Δ^9-THC seems to undergo a somewhat variable absorption from the gastrointestinal tract and to have a rather narrow 'therapeutic window' (dose range in which it is effective without producing significant unwanted effects). In one clinical study, for example Δ^9-THC was effective in one multiple sclerosis patient at an oral dose of 5 mg, whilst in a second multiple sclerosis patient it was effective only when the dose was raised to 15 mg (both 5 and 10 mg Δ^9-THC were ineffective in this patient) [29]. In another clinical study in which multiple sclerosis patients were given Δ^9-THC or placebo orally, both 2.5 and 5 mg Δ^9-THC were ineffective in producing subjective relief from spasticity, 7.5 mg was effective and 10 mg was intolerable to some of the patients [31]. Potential alternatives to the oral route include cannabinoid administration by rectal suppository [30], by aerosol/vapour inhalation [52–54] or by skin patch, all modes of administration that avoid first-pass metabolism of the absorbed drug. Other possibilities are direct application to the eye (for glaucoma) or spinal cord, use of the sublingual route and slow-release oral cannabinoid formulation.

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