DEVELOPING NEW MEDICINES FROM CANNABIS SATIVA: CHALLENGES AND PERSPECTIVES

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ABSTRACT

Objective. The aim of this paper is to critically review the medical applications of Cannabis sativa and related compounds.

Method. The text is based on the main articles on the discovery of the mechanisms through which cannabis exerts its effects, as well as on contemporary research trying to develop new medicines based on the endocannabinoid system.

Results. Despite the ancient use of Cannabis sativa, there have been very few applications of the herb in contemporary medicine. Nonetheless, the significant progress in this field, with the characterization of the endocannabinoid system in the brain, points to the possibility of developing new medications for the treatment of disorders of the central nervous system, such as anxiety, mood disorders and epilepsy.

Conclusion. The research on the pharmacological and therapeutic properties of Cannabis sativa and related compounds is a promising approach for drug development. However, this perspective must be tempered considering some potentially deleterious effects as well as the controversies that can be seen from social and political standpoints.

Key words. Cannabis sativa; pharmacology; anxiety; epilepsy.

INTRODUCTION

The herb Cannabis sativa has been used for centuries for recreational purposes due to its psychoactive properties.1–4 It has been known for diverse names, such as hemp, grass, pot, marijuana, maconha (in Brazil) among others. The drug is usually smoked and produces a typical constellation of psychological and behavioural effects, described as feelings of “high”, happiness and reduced anxiety, as well as relaxation, increased sociability, hallucinations,
amnesia, motor impairment and sedation. In addition to its non-medical use, there has been description of therapeutic effects of this plant since early times in human history. It has been proposed that cannabis might be effective as an analgesic, anti-seizure, anxiolytic and antidepressant, to mention a few.

Thanks to scientific development in this field in the last decades, there has been an ever-growing body of knowledge on the harmful and beneficial effects of this plant. Nonetheless, discussions on this subject have always been confounded by political views and ideological interests. Against this background, the authors provide a critical analysis on the medical advances in the field of cannabis research.

We summarize contemporary studies based on exciting scientific finds related to its pharmacology and clinical applications in psychiatric and neurological disorders.

METHOD

The present article reviews the scientific literature on the effects of Cannabis sativa and the underlying mechanisms. Indexed articles were selected in PubMed, published in English, focusing on preclinical and clinical aspects.

RESULTS

A search in PubMed database, with the term “cannabis”, revealed that the number of studies in which this herb is included has increased significantly in the last years (Figure 1). An interest in this field started to emerge at the beginning of the 90’s, possibly due to the discoveries regarding the actions of cannabinoids in the brain, as recapitulated below.

Discovering the mechanisms underlying the effects of Cannabis sativa

The first scientific advances on this field occurred by the middle of the last century, when the chemical constituents of Cannabis sativa could be finally identified. This plant has more than 60 chemical compounds, termed phyto cannabinoids, from which Δ⁹-tetrahydrocannabinol (Δ⁹-THC) is the most investigated and seems to account for the main effects induced by cannabis use. Another major component is cannabidiol (CBD), which also has promising therapeutic potentials.

Until the 70’s it was thought that cannabinoids would act similarly to general anesthetics, due to its lipophilic character, by dispersing the lipid bilayer of the plasma membrane. Nevertheless, this mechanism did not explain the very specific effects of Δ⁹-THC and its synthetic counterparts (termed synthetic cannabinoids), which are related to the dose used and dependent upon small changes on the molecular structures of these compounds. Thus, during the 80’s, researchers became convinced that specific receptors for cannabinoids might exist in brain. Indeed, this receptor was first identified in 1988 and cloned in 1990.

The characterization of a specific receptor for cannabinoids was a major breakthrough in understanding the effects of Cannabis sativa. Remarkably, its neuro-anatomical distribution is very much in line with the pharmacological effects of this herb (Figure 2), and could finally explain the molecular basis for Δ⁹-THC activity. In addition, a second receptor subtype was cloned soon thereafter, whose expression in brain is still a matter of debate. The IUPHAR (International Union of Basic and Clinical Pharmacology) named these receptors in the order of discovery in CB1 and CB2. Both CB1 and CB2 cannabinoid receptors are members of the superfamily of G-protein-coupled receptors, mediation by a Gi/o-coupled receptor and acted inhibiting adenylate cyclase.

CB1 is largely present in the central nervous system and accounts for most effects of cannabis/Δ⁹-THC. It is densely expressed in areas related with anxiety, stress, and reward, including prefrontal cortex, hippocampus, hypothalamus, amygdala, periaqueductal gray matter, as well areas related to motor control, such as the basal ganglia (Figure 2).

After the discovery of the CB1 receptors, a second major breakthrough was the identification of an endogenous agonist for this receptor. It was found that an arachidonic acid derivative, arachidonoyl ethanolamide (also termed anandamide, after ananda, a Sanskrit word for “bliss”), isolated from mammalian brain, could bind this receptor similarly to Δ⁹-THC. Thus, in addition to the phytocannabinoids and the synthetic cannabinoids, there were now the endocannabinoids, “the brain’s own marijuana”. Next, others endocannabinoids were described, including N-dihomo-gamma-linolenoyl ethanolamine, N-docosatetraenoylethanolamine, 2-arachidonoylglycerol (2-AG), and 2-arachidonoyl-glyceryl ether (noladin ether). The body’s natural agonists found in higher levels are 2-AG and anandamide. While anandamide has higher affinity by CB1 receptor, 2-AG has similar affinity for both CB1 and CB2 receptors.

Now it is known that endocannabinoids have peculiar neurophysiological properties. Contrary to
classical neurotransmitters, they are not stored in vesicles, being produced in post-synaptic neurons and acting upon CB1 receptors localized on presynaptic neurons. Therefore, endocannabinoids act as retrograde neurotransmitters and are released on demand in response to excessive neuronal activity (Figure 3). 9,13

The end of the endocannabinoids actions happens when they re-enter the nerve terminal. Although this topic is still controversial, several studies point to the existence of a membrane transporter that facilitates this process. 14,15 Once inside the neurons, endocannabinoids undergo metabolism by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), that hydrolyzes anandamide and 2-AG, respectively. 9 Altogether, the endocannabinoids, their receptors and the enzymes responsible for their synthesis, internalization and degradation constitute the endocannabinoid system (Figure 3).

The FAAH has become an important pharmacological target, since its inhibition enhances anandamide endogenous levels. Therefore, several compounds have been developed in order to potentiate the endocannabinoid system, such as URB-597. 16 Other pharmacological target is the MGL, which can be inhibited by the experimental compounds URB-602 or JZL-194.

Beyond these compounds, other synthetics drugs were developed, including arachidonoyl-2'-chloroethanolamide (ACEA), selective CB1 agonist; AM1241, selective CB2 agonist; WIN-55,212-2, non-selective agonist; SR141716A (Rimonabant), CB1 antagonist; SR144528, CB2 antagonist; AM404, UCM 707, VDM, endocannabinoid transport inhibitors.

Figure 1. Number of publications indexed in PubMed (www.pubmed.com) with the term "cannabis", in five-year periods, from 1951 to 2010.

Figure 2. Some of the main brain regions in which the cannabinoid receptor is expressed and their role in mediated the effects of Cannabis sativa.

Figure 3. Schematic representation of endocannabinoid system: N-arachidonoyl-ethanolamide (anandamide, AEA) and 2-arachidonoyl-glycerol (2-AG) are synthesized in a postsynaptic neuron and released after calcium influx (1). They bind to CB1 receptors in presynaptic neuron (2). AEA and 2-AG actions are terminated when they are captured by transporters (3) and then metabolized by Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), respectively (4).
The therapeutic relevance of Cannabis sativa, cannabinoids and other compounds that interfere with the endocannabinoid system

Despite the ancient interest in Cannabis sativa, this herb and its compounds are actually rarely employed in contemporary medicine. Δ9-THC is used as an anti-emetic, appetite promoter and analgesic, yet under very specific circumstances, as other medicaments are generally preferred.17,18

A more widely use for this compound emerged thanks to research with other phytocannabinoid, CBD. Early studies conducted in Brazil revealed that his substance could prevent some deleterious effects of Δ9-THC, including psychosis and anxiety, leading to investigations that unveiled interesting properties of CBD, including anxiolytic and antipsychotic.19 Furthermore, CBD has been used together with Δ9-THC in the treatment of multiple sclerosis. This medicine (trade name Sativex®; GW Pharmaceuticals) consists of extracts from Cannabis sativa grown to produced either compounds, which are them mixed at an approximately 1:1 ratio. It has been first approved in Canada and then in some European countries. Clinical studies have shown that it is devoid of major side effects, with moderate efficacy against symptoms of this disease.18

As for the synthetic analogs of Δ9-THC, they have not found their way into clinical practice, apart from a few specific uses, such as nabilone for reducing emesis and increasing appetite. A more promising strategy has been the development of substances that act through enhancement of endocannabinoid activity, rather than as direct CB1 agonists. As discussed above, the actions of the main endocannabinoid, anandamide, are terminated by a reuptake process followed by hydrolysis, inside neurons, by FAAH. Drugs that inhibit this enzyme promote an increase in the brain levels of anandamide and enhance CB1 receptor activity in a more subtle way, as compared to direct agonists.16 There are perspectives particularly as new strategies for the pharmacotherapy of psychiatric and neurological disorders.

Regarding the potential of these drugs for psychiatric disorders, they have been extensively investigated in animal models of anxiety and depression. Generally, these models measure the efficacy of a drug in changing the behavior of laboratory animals, so that they would explore an aversive environment or cope with punishing and stressful stimuli. Considering the calming, relaxing and rewarding effects of marijuana, it is not surprising that cannabinoids are effective in animal models used to studying and screening new anxiolytic drugs, whereas CB1 receptor antagonists have demonstrated anxiogenic and pro-depressive profiles.20 However, the effects of cannabinoids on experimental anxiety are generally complex, as low doses are normally anxiolytic and high doses tend to be anxiogenic, a problem further complicated by that fact that these drugs may impair locomotion. An interesting alternative to circumvent the complex effects of cannabinoids in these models has been the use of FAAH-inhibitors, such as URB-597. Thus, it has been consistently demonstrated this drug induces anxiolytic effects, similar to diazepam, in doses that do not induce motor impairment or memory loss.21-23 Furthermore, this FAAH inhibitor also alleviated the consequences of inescapable stressors in animal models, an effect similar to antidepressant drugs.24

The main problem with cannabinoids is that they may cause psychosis, addiction and tolerance, induce sedative effects, and impair learning and memory.18,25 In this context, FAAH inhibitors constitute a promising alternative.16,21-23,26 However, further studies are still required before these drugs may be tested in humans. First, we should still understand the precise role of endocannabinoid system in control of anxiety and mood disorders. Second, the long term effects of these drugs should be characterized in laboratory animals, since must studies have been performed with acute treatment. Finally, their putative side-effects, abuse potential and the toxicological profile should also be evaluated.

In the realm of the neurological practice, epilepsy is among the most severe disorders that affecting approximately 50 million people worldwide. Despite the therapeutic arsenal of the antiepileptic drugs, approximately 30% of patients with epilepsy show “pharmaco resistant epilepsy” and still suffer from seizures. Thus, the development of more effective antiepileptic drugs for patients with refractory seizures is undoubtedly necessary.27

The use of Cannabis sativa as an anticonvulsive agent dates back to 5000 years.1 In present days, it has been proposed that marijuana is protective against first onset seizures and in preventing tonic-clonic and partial seizures.28 However, the clinical efficacy of cannabinoid drugs as anticonvulsive agents for human epilepsy syndromes has not yet been conclusive. Additionally, other studies have revealed no effect or even increased seizure susceptibility with marijuana use.26
Despite the controversies regarding the cannabinoid drugs utilization for epilepsy treatment in humans, pharmacological researches have been addressing important roles for such substances in modulating both epilepsy and epileptogenesis. There has been evidence that endocannabinoids are synthesized on demand when neurons are stimulated, modulating neurotransmission and dampening neuronal activity. In other words, the endocannabinoid system might work as a sort of endogenous anti-seizure system.29

In experimental epilepsy, data regarding pro- or anticonvulsive effects of cannabinoids may depend on the model or dose tested. Both agonists and antagonists have indeed been studied for their modulatory properties on neuronal excitability. Δ9-THC, CBD and their analogs are generally effective in several models, displaying anti-epileptiform and anti-seizure actions in vitro and in vivo.30-32 In addition, recent studies have shown that cannabinoid agonists significantly enhanced the anticonvulsant action of carbamazepine, phenytoin, phenobarbital and valproate against maximal electroshock-induced seizures in mice.33,34

Conversely, CB1 receptor antagonists are known to be pro-convulsive through the increase of seizure frequency and through the decrease of seizure threshold during hyperexcitable state in mice.35 However, recent results have showed that single application of a given CB1 receptor antagonist following rat head injury prevents long-term hyperexcitability.36 In addition, CB1 receptor antagonism during experimental febrile seizures in rats prevents the emergence of febrile seizure as well as its susceptibility.37 The reasons for these apparently contradictory effects have not been yet fully elucidated.

As mentioned above, evidence suggests that production and release of endocannabinoids are shown to be increased in the central nervous system following seizures. By reducing neurons excitability and by activating intracellular signaling cascades, endocannabinoids provide protection against excessive neuronal activity, which support their involvement in seizure protection.29 Therefore, one promising strategy would be developing drugs that would enhance endocannabinoid activity and counteract seizure initiation and propagation, possibly through blockade of endocannabinoid-hydrolysis. Accordingly, our research group and others have observed clear anti-seizure effects of FAAH-inhibitors in animal models. In humans, recent studies performed in vivo positron emission tomography images of the type 1 cannabinoid receptor in patients with mesial temporal lobe epilepsy identified an increase in type 1 cannabinoid receptor availability at the seizure onset zone suggesting that changes in the endocannabinoid system modify excitability in different ways in the epileptic network, showing the relevance to elucidate the role of the endocannabinoid system in epilepsy and supporting the notion that this would be a promising approach for drug development.38

**DISCUSSION**

The present review summarized the progress regarding our understanding on the potential medical applications of *Cannabis sativa* and compounds that interfere with the endocannabinoid system, emphasizing that inhibiting endocannabinoid hydrolysis might represent a promising strategy for developing drugs for disorder of the central nervous system.

Nonetheless, the expectations must be balanced, since there are still several obstacles to be overcome, considering the social and political controversies surround the medical and recreational use of cannabis. This drug has been decriminalized in Brazil in 2006 and, recently, there has been a heated debate in this country on the legalization of its recreational use. The main medical concern on the wide use of this drug is the potential link with the development of psychiatric disorders. It has been argued, for instance, that long-term use may increase the risk for developing schizophrenia and cognitive impairment.39,40

In addition, even though this is a quite exciting field of research, it is mandatory that doctors and scientists avoid raising false perspective in the general public, as it is sometimes the case. In this sense, an interesting example was the short-lived marketing, three years ago, of rimonabant, an antiobesity drug. This drug was developed by Sanofi as an anti-obesity drug (trade name Acomplia), based on the logic that, since marijuana smoking increases appetite (as it has been known for millennia), a cannabinoid antagonist could be useful in treating obesity. Indeed, clinical trials revealed that this compound could reduce body weight in comparison to placebo (although the effect was modest, at the best).41 Nevertheless, data from these studies clearly revealed that this drug increased the risk of psychiatric side-effects, mainly anxiety and depression.41 Notwithstanding this problem, the drug was approved in some countries, including Brazil, by
the middle of 2008, under great expectation. By the end of the very same year, the company decided to remove this drug from the market worldwide, because many patients were complaining from an increase in anxiety, depression and suicidal thoughts, side-effects which were entirely expected since the beginning of the development of rimonabant. This “saga” provides an important lesson on how we should avoid raising expectations in the field of drug development.

Therefore, it can be concluded that there are promising researches regarding the potential medical use of Cannabis sativa and related compounds. However, science is not enough to approach several relevant questions in this controversial field, and there is a need for an interdisciplinary debate, covering also social and political aspects. In any case, the scientific approach is indispensable to advance medicine and tackle false promises, ideological discourses and distorted views.

DISCLOSURE

The authors have no conflict of interests to declare.

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