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Targeted Reviews

Cannabis, cannabidiol, and epilepsy — From receptors to clinical response

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ABSTRACT

Recreational cannabis use in adults with epilepsy is widespread. The use of cannabis for medicinal purposes is also becoming more prevalent. For this purpose, various preparations of cannabis of varying strengths and content are being used. The recent changes in the legal environment have improved the availability of products with high cannabidiol (CBD) and low tetrahydrocannabinol (THC) concentrations. There is some anecdotal evidence of their potential efficacy, but the mechanisms of such action are not entirely clear. Some suspect an existence of synergy or "entourage effect" between CBD and THC. There is strong evidence that THC acts via the cannabinoid receptor CB_1. The mechanism of action of CBD is less clear but is likely polypharmacological. The scientific data support the role of the endocannabinoid system in seizure generation, maintenance, and control in animal models of epilepsy. There are clear data for the negative effects of cannabis on the developing and mature brain though these effects appear to be relatively mild in most cases. Further data from well-designed studies are needed regarding short- and long-term efficacy and side effects of CBD or high-CBD/low-THC products for the treatment of seizures and epilepsy in children and adults.

Key questions

1. What is the role of the endocannabinoid system in response to cannabis and its compounds?
2. Does the epidemiology of cannabis use support developing cannabis and its compounds for the treatment of epilepsy?
3. What are the cognitive, psychosocial, and behavioral effects of cannabis and its compounds?
4. What is the evidence for efficacy of cannabis and its compounds for the treatment of human epilepsy?

1. Introduction

Despite the recent interest, there is nothing new or revolutionary about proposing the use of cannabis or its derivatives for medicinal purposes. The oldest known written reports on cannabis use come from China (Chinese Emperor Fu Hsi, ca. 2900 BC, mentioned cannabis as a medicine that possessed *yin* and *yang*; there are also written records on cannabis from Chinese Emperor Shen Nung from 2737 BC [1,2]). The first definite scientific documentation of *Cannabis sativa* uses for medical and ritual purposes obtained through recent archeological discoveries in China comes from circa 2500 years BC [3]. Similar uses – medicinal, religious, and recreational – have been reported over the following millennia from Asia, Africa, Europe, and North/Central America [4]. Reports of cannabis use for the management of seizures came from modern neurologists including O'Shaughnessy and Gowers [5,6]. What is truly new is the hype that cannabis and its products have generated in the last few years and the numerous, mainly anecdotal, reports of its efficacy for seizure control in patients with various, mostly catastrophic, epilepsies [7].

The modern history of cannabis in the United States started in the 17th century with the decree by King James that forced all property owners in the colony to grow 100 plants of hemp for industrial/export purposes (the word hemp indicates industrial use, and the words cannabis and marijuana imply medicinal and recreational uses) [1]. Throughout the mid-to-late 19th century, cannabis growth, processing, distribution, and use were ubiquitous. During those times, cannabis was used mainly for medicinal purposes, with the US Dispensatory in 1854 listing cannabis compounds as possible remedies for neuralgia, depression, pain, muscle spasms, etc. At that time, the main supplier of "Piso's Cure for Consumption" was Hazeltine Corporation in Warren, PA. At the request of the federal government via the "Pure Food and Drug Act", the name of their product was changed to "Piso's Cure" and, later, to "Piso's Remedy" for coughs and colds. It was thought to be a remedy for all ages as indicated in Norman Rockwell's advertisement that stated "Good for young and old" with multiple suggested uses. From then until the early 20th century, the use of cannabis plant products was not regulated. The first restrictions were introduced in 1906 by the "Pure Food and Drug Act". Between 1893 and 1894, the "Indian Hemp Drugs Commission" contracted by the British government produced a detailed report on the growth, production, uses, and abuses of cannabis products. Many

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of the same issues were addressed by the Commission as are being resurrected in America as well as around the world today [8]. Despite opposition from the American Medical Association (AMA) in 1937, the US government made it illegal to possess or transfer cannabis. Recently, the political climate has changed, and many states have introduced various pieces of legislation ranging from limited approval of high-cannabidiol (CBD) products for medicinal purposes (e.g., Carly's Law in Alabama) to complete legalization of cannabis use in an attempt to circumvent the federal law (e.g., Colorado). The majority of the public is in support of some form of legalization of cannabis use with the "Ending Federal Marijuana Prohibition Act of 2013 (H.R. 499)" introduced recently. Thus, the question is, "are we going to see a resurrection of medical (and other) cannabis use in the US in the next decade"? Since the answer is most likely "yes", given the current growth in medicinal and recreational uses in Colorado after legalization [9], as physicians, we need to understand the medical aspects of cannabis use. Therefore, this targeted review poses four key questions:

1. What is the role of the endocannabinoid system in response to cannabis and its compounds?
2. Does the epidemiology of cannabis use support developing cannabis and its compounds for the treatment of epilepsy?
3. What are the cognitive, psychosocial, and behavioral effects of cannabis and its compounds?
4. What is the evidence for efficacy of cannabis and its compounds for the treatment of human epilepsy?

2. Key questions

2.1. What is the role of the endocannabinoid system in response to cannabis and its compounds?

The evidence for the importance of the endocannabinoid system (ECS) as a potential target for the development of new antiepileptic drugs comes from animal rather than human studies. Before we address the role of the ECS in response to cannabis for the management of epilepsy, we need to understand the overall role of the system. Endocannabinoid system research began with the discovery of cannabinoid receptor-1 (CB_1) in 1988 [10,11]. Since then, a system composed of cannabinoid receptors CB_1 and CB_2, their endogenous ligands N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG), and various proteins that take part in their synthesis and removal has been described. Both CB_1 and CB_2 are metabotropic G-protein-coupled receptors. Their activation in response to excessive neuronal activity is dependent upon the "on-demand" synthesis of the AEA and 2-AG ligands [12,13]. The inactivation process of AEA and 2-AG is rapid, and it may include an intracellular facilitated transport mechanism, hydrolysis, or other currently unknown mechanism(s) [14]. The ECS is important for bioregulation as it takes part or is responsible for many processes such as inflammation, energy metabolism, immune regulation, memory, mood, and brain reward systems; overactivation of ECS may lead to obesity, type II diabetes, metabolic problems, and some forms of liver disease [15].

The cannabinoid receptors (CB_1 and CB_2) differ in their biological distribution and involvement. Cannabinoid type 1 receptors are predominantly located in the central (neocortex, hippocampus, basal ganglia, and cerebellum) and peripheral nervous systems with less pronounced expression in other tissues. By contrast, CB_2 receptors are located predominantly in the immune system with lesser density/representation in the central and peripheral nervous systems and in the gastrointestinal tract. The roles of these receptors are also divergent — CB_1 receptors are implicated in central food intake regulation, response to novelty and stress, addictive behavior, liver/gastrointestinal tract regulation, olfaction, and cardiovascular activity; the role of CB_2 receptors is less established, but overall, these receptors are thought to be mainly involved in immune regulation with lesser involvement in reward processing/addictive behavior and neurodegeneration.

Cannabis and its preparations such as marijuana smoke, kief, resin, oil, or tincture contain over 100 hydrocarbon compounds called "phytocannabinoids" [16]. The two most researched compounds are tetrahydrocannabinol (THC) and cannabidiol (CBD), with additional data available on several other cannabinoids including tetrahydrocannabivarin (THCV), cannabigerol, and cannabichromene [16,17].

Tetrahydrocannabinol and cannabidiol have been shown to be effective and have similar potency in the maximal electroshock model of epilepsy [18,19], but their mechanism of action was not elucidated until much later. A series of elegant experiments investigated the importance of ECS, THC, and CBD for the control of seizures in experimental models of epilepsy [20–22]. In the first set of experiments, these authors showed that both THC and CBD act as anticonvulsants in the maximal electroshock model of epilepsy and that the action of THC was mediated via the CB_1 receptor. The mechanism of action of CBD was different than that of THC and not elucidated in that study [22]. In the second set of experiments, the same authors solidified the role of the CB_1 receptor via testing the effects of AEA and AEA blockade in the same animal model of epilepsy and, again, showed strong anticonvulsant effect [21]. Finally, they showed, in the pilocarpine model of epilepsy (previously documented to resemble human focal-onset epilepsy), that THC and its analogue abolished seizures, while blocking the CB_1 receptor induced an epileptic condition similar to status epilepticus [20]. While these studies solidified the importance of the CB_1 receptor for the control of seizures, they also established that the antiepileptic mechanism of CBD is mediated via mechanism(s) different than the endocannabinoid system.

As indicated above, there is little doubt that CBD has antiepileptic properties. These properties have been studied in various animal models of epilepsy including the audiogenic [23], maximal electroshock [22,23], penicillin [24], pentylenetetrazole (PTZ) [25,26], pilocarpine [24], and transcorneal electroshock models [27] to show consistent antiepileptic effects. It is not clear how CBD exerts these properties. It has been proposed that CBD exerts its anticonvulsant effect via a polypharmacological profile and simultaneous modulation and/or prevention of neuronal hyperexcitability [24]. Multiple putative mechanisms of action of CBD have been discussed including effects on serotoninergic ($5HT_{1\alpha}$) receptors and NMDA receptors, regulation of Ca^{++} flow, enhancement of adenosine signaling, or interaction with GABA receptors (increased inhibition) [17,24,27–30]. These and other mechanisms of CBD's action may contribute to the synergistic or so-called "entourage" effects between CBD and THC and CBD's ability to reduce the psychoactive side effects of THC [16].

The current data not only support the role of the ECS in the generation and maintenance of seizures but also explain the positive effects of THC on seizure control in animal models of epilepsy. Further, the data support the notion that CBD is an effective and potentially potent anticonvulsant in animal models of epilepsy and that, through synergism with THC, it may exert direct and indirect effects on seizure control. Whether these or other effects will be observed in human epilepsy remains to be seen, but the results of animal studies appear to be in agreement with some of the anecdotal human data [28,31].

2.2. Does the epidemiology of cannabis use support developing cannabis and its compounds for the treatment of epilepsy?

According to the World Health Organization, approximately 2.5% (147 million) of the adult population worldwide uses cannabis for recreational or other reasons [32]. When used for medicinal purposes, cannabis is considered a complementary and alternative medicine (CAM) as it is not a mainstream or conventional therapy [33]. Approximately 40% of adults with epilepsy use or have used CAMs either because of lack of efficacy of the standard therapies, because of their side effects, or for other reasons. While the majority of CAMs are nonpharmacological (e.g., meditation, relaxation techniques, or stress