Published in final edited form as:

Expert Opin Pharmacother. 2015 ; 16(13): 1911–1914.

Cannabinoids: is there a potential treatment role in epilepsy?

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Abstract

Cannabinoids have been used medicinally for centuries, and in the last decade, attention has focused on their broad therapeutic potential particularly in seizure management. While some cannabinoids have demonstrated anticonvulsant activity in experimental studies, their efficacy for managing clinical seizures has not been fully established. This commentary will touch on our understanding of the brain endocannabinoid system's regulation of synaptic transmission in both physiological and pathophysiological conditions, and review the findings from both experimental and clinical studies on the effectiveness of cannabinoids to suppress epileptic seizures. At present, there is preliminary evidence that non-psychoactive cannabinoids may be useful as anticonvulsants, but additional clinical trials are needed to fully evaluate the efficacy and safety of these compounds for the treatment of epilepsy.

Keywords

cannabidiol; cannabinoids; clinical trials; endocannabinoid; epilepsy; phytocannabinoids; seizure; treatment

1. Historical perspective of medicinal marijuana

The use of the *Cannabis sativa* (marijuana) plant for both recreational and medicinal purposes has been dated as far back as the second millennia B.C. [1]. Of the more than 480 compounds present in *C. sativa*, over 100 have been identified as phytocannabinoids, lipid-soluble compounds that have varying degrees of pharmacological activity [2]. Δ(9)-tetrahydrocannabinol (THC) is the most prevalent phytocannabinoid in *C. sativa*, followed by the non-psychotropic constituent cannabidiol (CBD). Marijuana use causes many physiological effects throughout the body, with the most perceivable being its central psychotropic properties that are mediated, almost exclusively, by THC [1]. Over the last 60

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

years, experimental studies have demonstrated the anticonvulsant properties of cannabinoids in a number of *in vitro* and *in vivo* models of seizure [3]. Additionally, there have been a handful of clinical trials on cannabinoids efficacy as anticonvulsants, although a recent review revealed only four studies that fell within the inclusion criteria for acceptable randomized control trials [4]. The non-psychotropic cannabinoid CBD was found to produce a decrease in seizure occurrence, although the included studies were of low quality due to inadequate experimental design, small patient numbers and incomplete reporting of secondary outcomes (responder rate, quality of life measures and adverse effects). Furthermore, none of the four trials fulfilled the primary outcome of seizure freedom for 1 year or more [4]. Some epileptic patients have chosen to self-medicate with marijuana as a means to manage their condition, although this therapeutic effect is based purely on anecdotal data [5]. Historical and anecdotal evidence along with a resurgence of research supporting the medicinal benefits of cannabinoids has resulted in increased support for the use of medical marijuana for control of seizures. To date, in the U.S., legislation has been passed for the legalization/de-criminalization of medical marijuana in 25 states and the District of Columbia. However, there is a concern that the ongoing development of new strains of *C. sativa* containing increasingly higher levels of THC [6] may undermine its therapeutic potential and exacerbate adverse effects, including the potential for increased seizures [7,8] and psychosis [9]. In regard to the later effect, two recent cohort studies demonstrated that recreational cannabis use significantly increased incidence of psychosis [10] and was associated with a younger age of presentation [11], while acute THC poisoning following ingestion of high amounts of cannabis edibles was followed by an onset of severe psychosis in a recent case report on a 34-year-old Colorado woman [12].

2. Role of endocannabinoids in control of synaptic transmission

Discovery of the brain cannabinoid-type 1 receptor (CB1) was the initial trigger for many scientific studies, which revealed an intricate, widely expressed signaling system termed the brain endocannabinoid system (ECS), a spatially and temporally complex receptor system involved in the continuous regulation/fine-tuning of synaptic transmission [1,3]. Increasing levels of neuronal firing result in the ‘on-demand’ synthesis and release of the endocannabinoids anandamide or 2-arachidonylglycerol, which retrogradely activate presynaptic CB1, and are then rapidly removed via uptake/ degradative mechanisms. CB1 activation can result in both suppression of protein kinase A activity and induction of the mitogen-activated protein/extracellular signal-regulated kinases to modulate a multitude of downstream cellular processes and nuclear transcription pathways [13]. Additionally, inhibition of adenylate cyclase-induced cAMP production and protein kinase A activation, inhibition of voltage-gated Ca^{2+} channels and activation of inwardly rectifying K^{+} channels act as the primary mechanisms that underlie the ‘on-demand’ regulation of synaptic transmission via inhibition of vesicular neurotransmitter release. It is this dampening of excessive synaptic transmission by the ECS that underlies its function to tightly regulate excitatory and inhibitory synaptic transmission [3].

3. Cannabinoids as anticonvulsants: experimental and clinical findings

3.1 CB1-dependent anticonvulsant mechanisms

One of the mechanisms underlying the anticonvulsant properties of cannabinoids is through their activation of CB1. THC, as well as a number of synthetic cannabimimetics, has shown CB1-dependent anticonvulsant activity in experimental models of seizure and epilepsy [3]. In addition, experimental studies have demonstrated that antagonism of CB1 exacerbates seizure activity in the epileptic phenotype [3]. In regard to the previous findings, a clinical case report of considerable importance involved a 52-year-old individual with a history of adolescent idiopathic epilepsy who had been seizure-free for 20 years. Following inclusion into a treatment regimen for obesity with the CB1 antagonist rimonabant, this individual experienced new onset nocturnal partial seizures, which ceased and re-emerged following a hiatus and re-administration of rimonabant therapy [14]. These findings give evidence for CB1 agonism as a potential anticonvulsant therapy and that in the epileptic phenotype, the brain ECS acts to regulate seizure activity and neuronal hyperexcitability in a CB1-dependent manner.

The exclusive use of CB1 agonism as a therapeutic strategy is, however, unfeasible due to propensity for psychoactive effects, abuse potential and development of tolerance. In regard to the later effect, experimental studies have shown while CB1 activation is acutely anticonvulsant, prolonged exposure to cannabinoids result in exacerbation of seizure activity, most likely the result of receptor adaptation [15]. Several clinical cases involving the recreational or medical use of cannabinoids reported an increase in seizure severity following drug withdrawal, or first ever seizures while using cannabinoid-based medicines [7,8].

3.2 CB1-independent anticonvulsant mechanisms

CBD and its analog cannabidivarin (CBDV) are two phytocannabinoids that lack any direct CB1 agonist properties, and thus are non-psychotropic. Initial phase I clinical trials indicate that these phytocannabinoids are well tolerated with few adverse effects [4,16]. They have been reported to exhibit potent anticonvulsant activity in numerous experimental seizure models [2,3]. Although a few earlier clinical trials with CBD did not result in fulfilling the primary outcome of seizure control [4], interest in the anticonvulsant potential of these compounds was spurred by recent media events, including a case study involving a 5-year-old girl with Dravet syndrome experiencing treatment-resistant seizures. Her family sought an alternative treatment with an oil extract from a newly developed strain of *C. sativa* with a high CBD:THC ratio known as ‘Charlotte’s Web’ [17]. Her response to this therapy was remarkable in that several months into the treatment she had achieved a > 90% reduction in seizure frequency [17]. Shortly thereafter, many young epilepsy patients and their families sought to implement this alternative therapeutic strategy, even going as far as to moving to the state of Colorado for access to the CBD-enriched extract. Two recent papers presented data obtained by parent surveys representing a total of 94 children with refractory seizures that underwent self-treatment with the above CBD regimen. In the initial study involving a small cohort of patients, 42% (8 of 19) had a > 80% reduction in seizure frequency with CBD treatment [18]. The second parent survey from a larger cohort of 75 pediatric patients

indicated 38% of the cases achieved a > 50% reduction in seizures [19]. Additionally, both reports noted marked improvements in cognitive and motor function in patients undergoing the enriched CBD regimen. Of the range of seizure disorders included in these two surveys that showed a positive response to CBD, a majority of cases involved Lennox–Gastaut, Dravet and Doose syndromes [18,19]. As would be expected, the presentation of these findings over the last two years has evoked the attention of the neurological community, and is reflected by a number of recently published papers highlighted in the *Controversy in Epilepsy* section of the journal *Epilepsia* [17,20]. Over the past year, 13 U.S. States have passed specific legislation to legalize/ de-criminalize the use of cannabinoid-based medicines with a high ratio of CBD/THC for the treatment of seizure disorders.

Recently, findings from 10 centers approved for an FDA open-labeled trial of the pure CBD drug Epidiolex® (GW Pharma, U.K.) for treatment-resistant epilepsies were presented at the American Academy of Neurology 67th annual meeting (Washington, D.C., April 18 – 25, 2015). Evaluation from a total of 123 patients that received 12 weeks of continuous CBD therapy indicated an overall 46% decrease in seizure frequency from baseline, while patients with Dravet and Lennox–Gastaut syndromes showed a 51 and 52% suppression, respectively [21]. Importantly, a recent paper on the clinical findings of a subgroup from the above trials demonstrated a drug interaction of CBD with the anticonvulsant clobazam, as indicated by elevated plasma levels for clobazam and its active metabolite norclobazam, with an associated increase in side effects. This drug interaction likely resulted from inhibition of a specific cytochrome-P450 enzyme by CBD. Adjustment of clobazam dose alleviated patient side effects and returned clobazam plasma levels to baseline, although norclobazam levels remained significantly elevated, which the authors proposed may have counteracted the loss in clobazam levels following dose adjustment and possibly contribute to a synergistic anticonvulsant effect of CBD and clobazam [22]. These initial clinical studies indicate that CBD was well tolerated, showed potential as a therapeutic strategy for refractory seizures and likely improved functional and quality-of-life measures in patients with seizure disorders.

4. Expert opinion

The ECS is widely distributed throughout the CNS, underscoring its role toward regulation of both physiological and pathophysiological synaptic transmission, analogous to functioning as either the ‘automatic brake system’ or ‘emergency brakes’ of the brain, respectively. In both experimental and clinical epilepsy, plasticity of the brain ECS is evidenced by a long-lasting redistribution of forebrain CB1, which may function as a compensatory adaptation to control neuronal hyperexcitability [3]. This hypothesis is supported by experimental findings and observations in select clinical cases, whereby antagonism of CB1 results in exacerbation of seizure discharge [3,14].

Experimental findings have clearly demonstrated the anticonvulsant properties of exogenous cannabinoids, which are mediated by both CB1 and non-CB1-dependent mechanisms. This property of cannabinoids is supported by anecdotal observations that epileptics self-medicate with *C. sativa* to control their seizures [5], a perceived benefit that has contributed to the increasing support for the legalization of medical marijuana. Cannabinoid-based

anticonvulsants containing moderate levels of THC will unlikely be approved due to their adverse psychotropic effects, abuse potential and development of tolerance [1,2]. Consequently, self-medicating with *C. sativa* strains high in THC concentration may be contraindicated in the control of seizures due to the potential for maladaptive desensitization of CB1 function. Other experimental investigations directed toward targeting the brain ECS for seizure control include adjunctive therapy of CB1 agonists with established AEDs, targeting endocannabinoid uptake/degradative mechanisms, and modulating interactions/cross-talk of the ECS with other neuronal transmitter systems [3]. The anticonvulsant properties of the non-psychotropic cannabinoid, CBD, have been known for half a century, but only recently have they re-surfaced for their therapeutic potential towards the control of pediatric refractory seizures. Although a number of physiological effects of CBD in the brain have been identified, the mechanism(s) underlying its anticonvulsant properties are not yet understood.

Experimental and clinical findings reviewed above clearly indicate the anticonvulsant potential of targeting the ECS. Preliminary clinical findings demonstrate a therapeutic potential of CBD for the treatment of drug-resistant seizures disorders, and is a promising development. Continued research efforts are ongoing to increase our understanding of the brain ECS in hopes of developing novel therapeutic strategies for the treatment of epilepsy and other neurological conditions.

Acknowledgments

The work of the authors was supported in part by the National Institute of Neurological Disorders and Stroke and the CounterACT Program, National Institutes of Health Office of the Director (NIH OD); Grant Numbers: R21NS072061 and U01NS058213 to RJD.

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