Epilepsy & Behavior 70 (2017) 313–318

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Pharmacology of cannabinoids in the treatment of epilepsy

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ARTICLE INFO

Article history:
Received 17 October 2016
Revised 9 November 2016
Accepted 11 November 2016
Available online 10 January 2017

Keywords:
Cannabinoids
Tetrahydrocannabinol
Tetrahydrocannabivarin
Cannabidivarin
Tetrahydrocannabinolic acid
Pharmacology

ABSTRACT

The use of *cannabis* products in the treatment of epilepsy has long been of interest to researchers and clinicians alike; however, until recently very little published data were available to support its use. This article summarizes the available scientific data of pharmacology from human and animal studies on the major cannabinoids which have been of interest in the treatment of epilepsy, including Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), Δ9-tetrahydrocannabivarin (Δ9-THCV), cannabidivarin (CBDV), and Δ9-tetrahydrocannabinolic acid (Δ9-THCA). It has long been known that Δ9-THC has partial agonist activity at the endocannabinoid receptors CB1 and CB2, though it also binds to other targets which may modulate neuronal excitability and neuroinflammation. The actions of Δ9-THCV and Δ9-THCA are less well understood. In contrast to Δ9-THC, CBD has low affinity for CB1 and CB2 receptors and other targets have been investigated to explain its anticonvulsant properties including TRPV1, voltage gated potassium and sodium channels, and GPR55, among others. We describe the absorption, distribution, metabolism, and excretion of each of the above mentioned compounds. Cannabinoids as a whole are very lipophilic, resulting in decreased bioavailability, which presents challenges in optimal drug delivery. Finally, we discuss the limited drug-drug interaction data available on THC and CBD. As cannabinoids and *cannabis*-based products are studied for efficacy as anticonvulsants, more investigation is needed regarding the specific targets of action, optimal drug delivery, and potential drug-drug interactions.

This article is part of a Special Issue titled Cannabinoids and Epilepsy

Published by Elsevier Inc.

1. Introduction

There has long been interest in the use of *cannabis* products in the treatment of various medical conditions, including epilepsy. After centuries of anecdotal reports of improvement with *cannabis* products but limited human data to support their use, there has been a vast expansion of research (including recent double-blinded, placebo controlled trials) investigating the pharmacologic potential of various cannabis products as anti-epileptic drugs (AEDs). The *cannabis* plant (*Cannabis sativa*) consists of around 100 compounds known as phytocannabinoids, and the vast majority of research on *cannabis* products in the treatment of epilepsy has been done on the main psychoactive component, Δ9-Tetrahydrocannabidiol (Δ9-THC). There has been more recent interest in investigating those compounds which do not have psychoactive properties as potential AEDs [1], namely cannabidiol (CBD), but also including Δ9-tetrahydrocannabivarin (Δ9-THCV), cannabidivarin (CBDV), and Δ9-tetrahydrocannabinolic acid (Δ9-THCA). These phytocannabinoids are structurally similar (see Fig. 1), but differ in regards to their pharmacology and actions by which they have anticonvulsant effect. Here, we summarize the literature to date on the mechanisms of action, metabolism, and interactions of the above listed major phytocannabinoids, in order to gain a better understanding of the proposed pharmacology of *cannabis* products which have potential for the treatment of epilepsy.

2. Mechanism of action

2.1. Δ9-THC

The pharmacology of Δ9-THC is perhaps the best understood of all the phytocannabinoids and has been studied extensively since its synthesis in 1964 [2]. The compound is responsible for the main psychotropic effects of *cannabis* and use of synthetic, high-affinity analogues led to the discovery of its CNS targets and identification of the

Abbreviations: (AED), Anti-epileptic drug; (THC), Δ9-Tetrahydrocannabidiol; (CBD), cannabidiol; (Δ9-THCV), Δ9-tetrahydrocannabivarin; (CBDV), cannabidivarin; (Δ9-THCA), Δ9-tetrahydrocannabinolic acid; (TRP), transient receptor potential; (VGCC), voltage gated calcium channel; (VGSC), voltage gated sodium channel; (VGKC), voltage gated potassium channel; (PPARγ), peroxisome proliferator-activated receptor gamma; (DLGα), diacylglycerol lipase alpha; (COX), cyclooxygenase.

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http://dx.doi.org/10.1016/j.yebeh.2016.11.016
1525-5050/Published by Elsevier Inc.

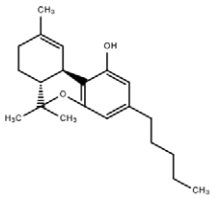
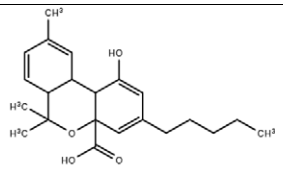
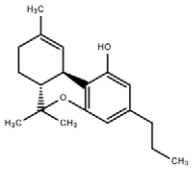
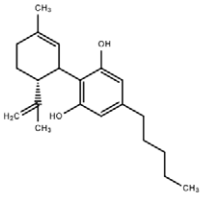
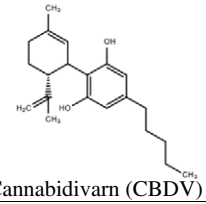
Chemical Structure	Potential Targets of Action in Epilepsy
 Δ9-tetrahydrocannabidiol (THC)	CB1 CB2 TRPA1 TPRV2 TRPM8 GPR55 5-HT_{3A} PPARγ μ- and δ-opioid receptors β-adrenoreceptors VGCC, VGKC, VGSC
 Δ9- tetrahydrocannabinolic acid (THCA)	TRPA1 TRPV4 TRPM8 DLGα COX 1, COX 2
 Δ9- Tetrahydrocannabivarin (THCV)	CB1 CB2 GPR55 TRPA1 TRPV1-4
 Cannabidiol (CBD)	TRPV1 VGCC, VGSC 5-HT_{1A}, 5-HT_{2A} GPR55 Adenosine receptors A_1 and A_2 VDAC1 TNFα
 Cannabidivarn (CBDV)	CB1 and CB2 – independent – more data needed

Fig. 1. Chemical structures of major phytocannabinoids and their possible targets by which they exert anticonvulsant effects.

endocannabinoid system [3,4]. The best studied targets of Δ9-THC are the endocannabinoid receptors, CB1R and CB2R, where it serves as a partial agonist at sub-micromolar concentrations [5]. Primarily found in the presynaptic terminals of CNS neurons, CB1 receptors are highly expressed in limbic structures (amygdala, hippocampus, cingulate), cerebral cortex, basal ganglia and select areas of the midbrain and medulla [6] and are a G-protein-coupled receptors which can modulate neurotransmitter release. Synaptic activity modulates the on-demand synthesis of anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), the endogenous ligands for the CB-receptors in the post-synaptic terminal and this signaling mechanism mediates several forms of short- and long-term synaptic plasticity [7]. The crystal structure of the CB1 receptor has recently been described, which may facilitate the design of the new CB1 receptor ligands for therapeutic use [8]. The major expression of CB2 receptors is in peripheral immune tissues such as the spleen, lymph nodes, and bone marrow as well as on B-cells, macrophages, and microglia where activation may lead to immunosuppressive responses [9]. There is also limited CB2-receptor expression in CNS neurons including in the brainstem [10] and hippocampus [11] where activation can affect neuronal excitability. In addition to its effects on the canonical endocannabinoid receptors, Δ9-THC binds to and modulates several other receptor targets in submicromolar or micromolar concentrations including the transient receptor potential (TRP) cation channels TRPA1, TRPV2, and TRPM8; the orphan G-coupled protein receptor GPR55; 5-HT_{3A} receptor; the peroxisome proliferator-activated receptor gamma (PPARγ); μ- and δ-opioid receptors, β-adrenoreceptors, some subtypes of *Ca*, K and Na channels [5]. The functional consequences of activation of these targets by Δ9-THC *in vivo* are not completely understood.

Even before the pharmacology of Δ9-THC was delineated, *in vivo* and *in vitro* studies demonstrated that the compound may have effects on experimental models of seizures. Many of the studies in acute seizure models demonstrated anticonvulsant effects of Δ9-THC or modulation of anticonvulsant effects of traditional anti-seizure drugs though others demonstrated no effects, mixed effects or proconvulsant effects [1]. There is CB1-receptor expression in human and experimental epilepsy

[12]. The anti-seizure effects of synthetic CB1-receptor blockers and modulators of endocannabinoid metabolism have also shown anticonvulsant effects in some but not all studies [1,13]. The mixed results in seizure and epilepsy models of Δ9-THC and its analogues likely reflects the complicated pharmacology of the compound as well as the diverse effects of endocannabinoid signaling in the CNS, including impact on both GABAergic and glutamatergic signaling [12]. Furthermore, there is evidence of homeostatic control of CB1-receptor expression and effects in acute seizure models may differ from chronic models. Downregulation of CB1-receptor expression with chronic activation may alter drug targets or change the functional impact of Δ9-THC. Only one case series of 5 patients examined the effects of isolated Δ9-THC in human epilepsy [14] and most case reports and case series suggesting efficacy have used extracts from *cannabis* or other preparations containing other cannabinoids [15].

2.2. Δ9-THCA

Delta-9-tetrahydrocannabinolic acid (Δ9-THCA)is the metabolic precursor of Δ9-THC, and it is found in high concentrations in living *cannabis* plants. It is decarboxylated to Δ9-THC through drying or burning of the plant and it is thought to have little psychoactive properties. *In vitro* experiments have demonstrated activation of TRPA1 and TRPV4 channels and blockade of TRPM8 channels at low micromolar concentrations. It inhibits diacylglycerol lipase alpha (DLGα, the key biosynthetic enzyme for the endocannabinoid 2-AG) and cyclooxygenase-1 and 2, albeit at concentrations > 10 μM [16]. Little is known about the effects of this compound on epilepsy though there are anecdotes and claims on the internet suggesting anti-seizure effects [17].

2.3. Δ9-THCV

Delta-9-tetrahydrocannabivarin (Δ9-THCV) is another cannabinoid found in cannabis in varying amounts. Like Δ9-THC, it is a partial agonist of CB1/2 receptors and has some activity on GPR55, TRPA1 and TRPV1–4 receptors at submicromolar or low micromolar concentrations [5]. One study has shown anti-seizure effects in *in vitro* and *in vivo* animal models [18].

2.4. CBD

Unlike Δ9-THC, CBD has a very low affinity for the endocannabinoid receptors by which Δ9-THC exerts its most meaningful anticonvulsant effects [19]. A series of experiments showed the anticonvulsant properties of THC and CBD in the maximal electroshock and pilocarpine models of epilepsy, elucidated that the anticonvulsant activity of THC was modulated by its actions on the CB1 receptor, and that the mechanism by which CBD has anticonvulsant properties was different [20–22]. Therefore, research on CBD mechanisms has mainly been focused on CB1- and CB2-dependent mechanisms of action.

To date, a number of proposed mechanisms of action for CBD with potentially anticonvulsant properties have been identified, though the exact mechanism by which CBD possesses anticonvulsant activity remains unknown. Cannabidiol acts as an agonist at human TRP channels, specifically in the TRPV1 channel, which is in part responsible for calcium channel modulation [23,24]. How the TRPV1 channel may be involved in epilepsy and thus how this action of CBD may carry anticonvulsant effects is less clear [25]. Currently, there is not enough evidence to support that CBD's agonist activity at TRPV1 can account for its anticonvulsant effect [26].

Cannabidiol has a number of actions on ion channels which are targeted by other anti-seizure drugs. Cannabidiol blocks human T-type voltage gated calcium channels (VGCC) [27]. These low voltage-activated channels are also blocked by a select number of AEDs such as zonisamide and ethosuximide, though others such as levetiracetam, lamotrigine, and eslicarbazepine target other VGCCs (L-, P/Q-, and N-type) [28].

Cannabidiol also has voltage gated sodium channel (VGSC) blocking abilities *in vitro*, but this action does not appear to necessarily confer an anticonvulsant effect *in vivo*. Recent research has indicated that CBD can preferentially target resurgent sodium currents over peak transient currents generated by both wild-type Nav1.6 as well as the aberrant resurgent and persistent current generated by Nav1.6 mutant channels (which can be seen in syndromic epilepsies such as Dravet Syndrome) [29]. Given that recent Phase 3 Trials of CBD for the treatment of both Dravet and Lennox-Gastaut Syndrome [30,31] have been completed, the action on VGSCs should certainly be investigated further and is a plausible mechanism of action by which CBD exerts anticonvulsant properties in these disorders.

Other potential mechanisms for CBD's anticonvulsant abilities include modulation of various receptors. Cannabidiol exhibits affinity for serotonin receptors 5-HT_{1A} and 5-HT_{2A}. Though this is not a conventional target for AEDs, the drug fenfluramine (which is a potent 5-HT releaser activating multiple 5-HT receptor subtypes, including 5-HT_{2A}) may be an effective treatment for seizures in Dravet Syndrome [32,33]. Other suggested mechanisms of CBD which could be anti-epileptogenic include antagonism at G-coupled protein receptor protein 55 (GPR55), modulation of adenosine (A_1 and A_2) receptors, voltage-dependent anion-selective channel protein 1 (VDAC1), and tumor necrosis factor alpha (TNFα) release, though more data are needed in order to determine not only CBD's action on these but also the role they may play in epilepsy and other medical conditions [34–37].

2.5. CBDV

Very little data exist on the proposed mechanisms of action of CBDV (the propyl variant of CBD), though it is presumed its actions are similar to CBD. Of importance, however, is that CBDV in isolation has been shown to have anticonvulsant properties in maximal electroshock and audiogenic seizure models in mice and PTZ and pilocarpine-induced seizures in rats [38]. And, though specific mechanisms for CBDV's anticonvulsant properties have not yet been elucidated beyond its chemical similarity to CBD, CBDV's mechanism also seems to be CB receptor-independent. A study comparing the anticonvulsant activity in *cannabis*-derived botanical drug substances (BDSs) rich in CBDV but also containing THC and purified CBDV showed that the BDSs had greater affinity to the CB1 receptor than the purified CBDV [39].

3. Metabolism

3.1. THC

The pharmacokinetics of Δ9-THC are perhaps best studied of all the phytocannabinoids. Absorption of Δ9-THC is significantly dependent on the route of administration. Smoked Δ9-THC has a bioavailability of ~25% with a rapid time to peak plasma levels (6–10 min). Inhaled or vaporized Δ9-THC has similar absorption and single dose kinetics with bioavailability of 10–35% reported in the literature. Oral administration has a bioavailability of ~6% and variable though solutions with sesame oil or glycocholate may show improved absorption. Time to Cmax is much longer than for smoked or vaporized Δ9-THC, between 2 and 6 h [40]. Sublingual administration using an oral mucosal spray such as nabiximols, show similar bioavailability and single dose kinetics as oral Δ9-THC though perhaps with less variability [41].

Highly lipophilic, Δ9-THC is rapidly distributed throughout the body. The volume of distribution is estimated to be 3.4 L/kg and 95–99% is protein-bound [42]. Significant amount of Δ9-THC is stored in adipose tissue where it can be slowly released in the blood over days in chronic users [43]. Δ9-THC can also cross the placenta [40].

Δ9-THC is hydroxylated in the liver by CYP2C9, 2C19, and 3A4 isozymes into 11-OH-THC which is then further transformed to over 30

metabolites. In addition, glucoronidation is responsible for most of the phase II metabolism of Δ9-THC. About 65% of Δ9-THC metabolites are excreted in the feces and 25% in the urine. There is also evidence of extrahepatic metabolism of Δ9-THC in tissues that express cytochrome P450 enzymes such as the brain [42]. The terminal half-life of Δ9-THC is estimated to be 25–36 h [44].

3.2. Δ9-THCA and Δ9-THCV

Little is known about the pharmacokinetics of Δ9-THCA and Δ9-THCV in humans though a phase II trial of Δ9-THCV in patients with type II diabetes was recently completed (NCT02053272).

3.3. CBD/CBDV

Like Δ9-THC, CBD and CBDV have low water solubility and poor oral bioavailability, estimated to be 6% in humans [45], making oral administration less than favorable. This is due to significant first-pass metabolism in the liver and erratic absorption from the gastrointestinal tract leading to unreliable pharmacokinetics [34]. Despite this, CBD and CBDV have relatively rapid absorption with peak concentrations seen around 2 h after oral administration in animal pharmacokinetic studies [46]. Cannabidiol has and is being delivered in oil-based capsules and oil-based suspensions in human studies, notably the sesame oil-based suspension Epidiolex®. Other routes of administration of CBD for pain indications have been investigated including nasal, sublingual, and transdermal application. In an animal study, intranasal CBD was absorbed within 10 min with a bioavailability of 34–46%, and steady state plasma concentrations were achieved with transdermal gel application at a mean of 15.5 h [47].

Cannabidiol has a high volume of distribution (approximately 32 L/kg), and is very lipophilic and highly protein-bound, which dictates its pattern of distribution. There is rapid distribution to brain and adipose tissue and about 10% is bound to red blood cells [48]. Given its lipophilicity, concern has been raised regarding the possibility of accumulation over time with chronic use, especially in those with high adiposity [34].

Like other cannabinoids, CBD is hepatically metabolized, with extensive involvement of the cytochrome P450 system. After absorption, it is rapidly hydroxylated to 7-OH-CBD. The enzymes CYP2C19 and CYP3A4 are primarily responsible for the hydroxylation, with potential involvement of CYP1A1, CYP1A2, CYP2C9, and CYP2D6 [49]. 7-OH-Cannabidiol is then further metabolized by the liver and then these metabolites are excreted in the feces, with a small portion being excreted in the urine. Half-life in humans is estimated to be 18–32 h [48]. Metabolism data on CBDV are scant, but in an animal pharmacokinetic study, the half-life was noted to be similar to that of CBD [46].

4. Interactions

4.1. Δ9-THC

Because it is primarily metabolized by CYP2C9, 3A4 and, to a lesser extent, 2C19, drugs which induce or inhibit these cytochrome P450 isozymes may affect Δ9-THC metabolism. For instance, coadministration of valproate, a potent CYP2C9 inhibitor, can theoretically potentiate the psychotropic effects of Δ9-THC by decreasing plasma clearance.

Some *in vitro* evidence exists that Δ9-THC is an inhibitor of CYP2C9, 2C19, 3A4, and 1A2 at concentrations of 26–44 μM [50,51] though one *in vitro* study demonstrate that Δ9-THC increased the metabolism of phenytoin, a CYP2C9 substrate [52]. The clinical significance of this inhibition in humans is not known and there were no significant drug-drug interactions reported in the clinical development of nabixamols, which contains 50% 9-THC [51]. However, there are no human data on the impact of Δ9-THC on serum anti-seizure drug levels.

4.2. CBD

Cannabidiol has a potent effect on particular CYP enzymes, which could have implications for pharmacologic interactions with other medications (particularly AEDs). CBD has been shown to be a potent inhibitor of CYP2C19, CYP2D6, and CYP2C9, and may inhibit members of the CYP3 family [28,49,53,54]. Repeated administration of CBD may induce members of the CYP2B family in animal models [34]. No interaction data exist on CBDV.

To date, there are little data on drug interactions with CBD, particularly in humans. A pharmacodynamics animal study using maximal electric shock and audiogenic seizure models showed that CBD potentiated the anticonvulsant effects of phenytoin by two-fold, and modestly potentiated the effect of phenobarbital. Cannabidiol also reduced the anticonvulsant properties of chlordiazepoxide, clonazepam, and ethosuximide [55]. A recently published article revealed a clear drug-drug interaction between CBD and clobazam in a group of 13 pediatric patients. Clobazam and *N*-desmethylclobazam (active metabolite of clobazam) levels increased in response to increasing doses of CBD, and subjects more frequently reported sedation [56]. This interaction was also identified in a group of 11 adults and 6 children taking concomitant CBD and clobazam in an open-label study [57] Interactions with other AEDs have not been investigated, though one could hypothesize that AEDs which are metabolized by enzymes that are induced or inhibited by CBD could be affected. Once potential interactions are identified, they then need to be evaluated in the clinical setting to determine if they are clinically significant.

5. Conclusion

There is accumulating evidence that some cannabinoids have anticonvulsant properties in animal models of seizures and emerging evidence for efficacy in human epilepsies. Despite this empiric evidence, the mechanisms by which these compounds exert anti-seizure effects are poorly understood. The major cannabinoids have multiple targets within the CNS and can modulate activity of neurons, glia, and microglia and it is unknown which mechanism(s) are critical for therapeutic actions. The pharmacokinetic properties of Δ9-THC, Δ9-THCA, Δ9-THCV, CBD, and CBDV also present unique challenges to use as therapeutic agents including low bioavailability and potentially erratic absorption in oral formulations, significant accumulation in adipose and other tissues, and interactions with other drugs metabolized by the cytochrome P450 system. Some of these problems may be overcome by novel delivery systems (oromucosal, transdermal) or through synthesis of related compounds with optimized properties. However, the potential interactions with other anti-seizure drugs pose a particular problem for patients with treatment-resistant epilepsy for whom polypharmacy is the norm. For instance, in the case of clobazam, effects on the metabolism of the metabolite *N*-desmethylclobazam may potentiate medication side effects or confound interpretation of efficacy results [26,56] Finally, as the recreational use of *cannabis* expands, it will become more important to understand how compounds in the plant may affect therapeutic agents and better screening, counseling and monitoring will be necessary.

Disclosures

Dr. Gaston receives salary support from the State of Alabama (Carly's Law) for her work in the UAB CBD program, an open-label study of CBD in the treatment of refractory epilepsy.

Dr. Friedman receives salary support for consulting and clinical trial related activities performed on behalf of The Epilepsy Study Consortium, a non-profit organization. Dr. Friedman receives no personal income for these activities. NYU receives a fixed amount from the Epilepsy Study Consortium towards Dr. Friedman's salary. Within the past year, The Epilepsy Study Consortium received payments for

research services performed by Dr. Friedman from: Alexza Pharmaceuticals, Acorda, Eisai Medical Research, Pfizer, Upsher Smith, and Zynerba. He has also served as a paid consultant for UCB, Inc. and LivaNova as well as participated in advisory boards for GW Pharmaceuticals and Supernus. He has received honorarium from Neuropace, Inc. He receives research support from UCB, Inc., NINDS, CDC, and the Epilepsy Foundation.

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