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The Pharmacological Basis of Cannabis Therapy for Epilepsy

Doodipala Samba Reddy and Victoria M. Golub

Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M Health Science Center, Bryan, TX 77807, USA

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***Address correspondence to:**

D. Samba Reddy, Ph.D., R.Ph., FAAPS, FAAAS
Professor
Department of Neuroscience and Experimental Therapeutics
College of Medicine
Texas A&M University Health Science Center
8447 State Highway 47, MREB Building 2008
Bryan, TX 77807-3260, USA
Tel: 979-436-0324
E-mail: reddy@medicine.tamhsc.edu

Section: Neuropharmacology

ABBREVIATIONS:

CBD, cannabidiol; THC, Δ^9 -tetrahydrocannabinol; CNS, central nervous system; CB₁, cannabinoid receptor type 1; CB₂, cannabinoid receptor type 2; CBDV, cannabidivarin; AEDs, antiepileptic drugs; TRPV, transient receptor potential vanilloid; FAAH, fatty acid amide hydrolase; 2-AG, 2-arachidonoyl glycerol; AEA, N-arachidonylethanolamine.

ABSTRACT

Recently, cannabis has been suggested as a potential alternative therapy for refractory epilepsy, which affects 30% of epilepsy patients including children who do not respond to current medications. There is a large unmet medical need for new antiepileptics for refractory epilepsy and conditions associated with refractory seizures that would not interfere with normal function. The two chief cannabinoids are delta-9-tetrahydrocannabinol, the major psychoactive component of marijuana, and cannabidiol (CBD), the major non-psychoactive component of marijuana. There are claims of clinical efficacy of CBD-predominant cannabis or medical marijuana for epilepsy, mostly from limited studies, surveys or case reports. However, the mechanisms underlying the antiepileptic efficacy of cannabis remain unclear. This article highlights the pharmacological basis of cannabis therapy, with an emphasis on the endocannabinoid mechanisms underlying the emerging neurotherapeutics of CBD in epilepsy. CBD is anticonvulsant, but it has a low affinity for the cannabinoid CB₁ and CB₂ receptors; therefore the exact mechanism by which it affects seizures remains poorly understood. A rigorous clinical evaluation of pharmaceutical CBD products is needed to establish the safety and efficacy for the treatment of epilepsy. Identification of mechanisms underlying the anticonvulsant efficacy of CBD is additionally critical to identify other potential treatment options.

Introduction

Epilepsy is a chronic hyperexcitability disease that stems from various defects in neuronal networks in the brain, leading to recurrent seizures. Epileptic seizures are abnormal electrical discharges which can originate from a variety of brain regions and can cause alterations in behaviors, consciousness, and sensations. Epileptogenesis is the process by which a normally functioning brain becomes progressively epileptic due to an injury or other such risk factors as stroke, infection or prolonged seizures. Epilepsy may also develop due to an abnormality in neuronal wiring, an imbalance between excitatory and inhibitory neurotransmitters, or even a combination of these dynamics. In epilepsy patients, spontaneous seizures arise from an over excited and hypersynchronous neural network and generally involves both cortical and subcortical structures. Due to the large variation in types of epilepsy, it is classified as a spectrum disorder. Epileptic seizures can be classified into partial or generalized seizures. Partial seizures begin focally in a cortical site of the brain and account for approximately 60% of all epilepsies; whereas, generalized seizures involve both hemispheres from the onset of epileptogenesis and account for the remaining 40% of epilepsy types (Duncan et al., 2006; Reddy, 2014). Epilepsy can be further divided into two groups: primary and secondary. Primary epilepsy (50%) is idiopathic (unknown cause). Secondary epilepsy (50%), also referred to as acquired epilepsy, may result from a number of conditions including neurotoxicity, traumatic brain injury, anoxia, metabolic imbalances, prolonged seizures due to drug withdrawal, tumors, or encephalitis (Reddy, 2014).

Epilepsy affects about 65 million people worldwide with an incidence of 20-70 new cases per 10,000 individuals (Hesdorffer, 2013; Barrese, 2010; Rektor et al., 2015). The disorder has devastating effects on one's life, not solely as a direct result of the clinical implications, but also socioeconomic consequences such as social isolation, educational difficulties, unemployment, and stigmatization. These social consequences often result in the high comorbidity of epileptic patients with psychiatric disorders, such as depression, and an increased suicide rate (Kros, et al., 2015). The majority of new epilepsy diagnoses occur most frequently in children and the elderly. To date, no drug therapies exist for curing epilepsy; however, symptomatic relief can be found for up to 70% of patients. Antiepileptic drugs (AEDs) are the mainstay to achieving symptomatic seizure control; however, only two-thirds of epilepsy patients can be successfully treated by current AEDs (Iannotti et al., 2014). For the remaining 30% of epileptic patients, who suffer from intractable seizures that

cannot be controlled by antiepileptic medications, treatment is often invasive, requiring surgical resection or neurostimulation.

There is a large unmet need for novel therapies that provide effective control of drug-resistant or refractory epilepsy and would not interfere with normal function (Perucca and Gilliam, 2012; Friedman and Devinsky, 2015). This task is more challenging in certain types of devastating pediatric epilepsy, such as Lennox-Gastaut, Doose, and Dravet syndromes. Recently, cannabinoids have been suggested as potential therapeutic alternatives for some patients with refractory seizures. Emerging experimental and pilot clinical studies suggest that cannabidiol, a non-psychoactive constituent found within the cannabis plant, may act as an effective antiepileptic agent. The social media has created a lot of awareness and information sharing. There are many advocacy groups, including parents of children with refractory epilepsy, advocating CBD treatments and additional optional strategies. With the increase in preclinical data and publicized cases of cannabidiol-enriched strains of medical marijuana, advocacy groups have become more vocal about the possibility of cannabis use for the symptomatic treatment of epilepsy, especially within groups of parents with children who continue to experience refractory seizures. This article highlights the pharmacological basis of cannabis use for refractory epilepsy.

Marijuana, or cannabis, has been used since the 19th century for controlling epileptic seizures (Gowers, 1881). Marijuana is a colloquial term given to the dried flowers, stems, and leaves of a 1-5 meter weed which originating from Asia. Cannabis belongs to the plant family *Cannabaceae*, of which there are three main species which can differ in biochemical components: *Cannabis sativa*, *Cannabis indica*, and the lesser known *Cannabis ruderalis* (Baron, 2015). The cannabis plant contains over 200 compounds, referred to as cannabinoids (ElSohly and Gul, 2014). Among these are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD), which have been the focus of recent studies. THC has potent psychoactive effects, including causing feelings of euphoria and altered sensory perception. Withdrawal symptoms, such as irritability and disturbances in sleep, result with abrupt discontinuation of long-term use of THC. Thus, THC is classified as a schedule I controlled substance (high abuse potential and little medical use). Efforts to develop therapeutic agents based on THC yielded dronabinol (*Marinol*), which is used clinically for the control of nausea and moderate pain in cancer therapeutics. The unwanted psychoactive effects and withdrawal symptoms experienced by long-term use make THC a less likely option as a therapeutic option for epilepsy. CBD, however, is another major component of cannabis and does not exert psychoactive effects.

Products containing concentrated CBD have been suggested to be helpful for refractory seizure control (Blair et al., 2015). The targeted actions of CBD in the brain are complex, involving both neuronal and non-neuronal targets, thus the pharmacological mechanisms of CBD treatment in epilepsy have yet to be fully elucidated. Molecular targets of THC and CBD, as well as some of the actions exerted by these compounds are listed in Table 1.

Experimental and Clinical Studies of Cannabis in Epilepsy

There is a growing awareness about medical marijuana and CBD-enriched products. Historically, China had been using marijuana to treat rheumatism, pain, and convulsions (Maa and Figi, 2014). The use of marijuana was once not as politically-charged as it is now. The prohibition movement of America, beginning at the turn of the 20th century, started the ban on several drugs including cocaine, opium, and marijuana. Cannabis was available over-the-counter in the United States up until 1941, following the ratification of the Marijuana Tax Act of 1937, which restricted access to it. The Controlled Substance Act of 1970 classified cannabis as Schedule I, making its distribution and use illegal (Mechoulam, 1986). After the Controlled Substance Act of 1970 was passed, the testing and research of medical marijuana and its constituents was heavily controlled, therefore making experimentation more difficult.

Currently, the FDA has not yet approved the use of medical marijuana for any indication, however; 23 states and Washington D.C. have made provisions for the use of cannabis as a therapeutic agent for some conditions. Additionally, 4 states (Alaska, Colorado, Oregon and Washington) have also legalized recreational use of marijuana. This has led to burgeoning interest in the therapeutic potential of medical marijuana and its major constituents. Though the majority of cannabis research investigates the use of specific cannabinoids, limited array of studies show clinically significant evidence of analgesic effects from smoking or ingesting whole plant marijuana. The primary focus of these studies is to provide symptomatic relief of neuropathic pain. Two FDA-approved prescription cannabinoids are currently available for the treatment of chemotherapy-induced nausea and vomiting: dronabinol (*Marinol*) (a synthetic Δ^9 -THC) and nabilone (*Cesamet*) (a Δ^9 -THC congener). Sativex, a clinical medication that combines both THC and CBD has been investigated for the alleviation of neuropathic pain for those adults suffering from multiple sclerosis, and for symptomatic relief of cancer pains (Pertwee, 2012). There are currently two cannabis based products, with a high CBD content, being tested in clinical trials for refractory epilepsies such as Dravet Syndrome and Lennox-Gastaut: Epidiolex and Realm Oil. Epidiolex is an oil based product

with > 98% CBD and < 3% THC. Realm Oil is an extract of a strain of medical marijuana with a CBD ratio of 16:1. Neither product has been approved by the FDA or any other national regulatory agency.

Experimental Studies

Cannabinoids have antiepileptic effects in animals (Blair et al., 2015). CBD and its variants have been tested in several animal epileptic models including: maximal electroshock (Hill et al., 2012; Jones et al., 2015), pentylenetetrazol (Jones et al., 2010, Hill et al., 2012, Hill et al., 2013), pilocarpine (Jones et al., 2012, Hill et al., 2013), penicillin (Jones et al., 2012) audiogenic seizures (Hill et al., 2012, Hill et al., 2013), 6-Hz (Jones et al., 2015), subcutaneous metrazol threshold test (Jones et al., 2015) and cobalt implantation (Santos et al., 2014). In most of these paradigms, CBD consistently showed anticonvulsant effects. Additionally, Jones et al (2015) assessed CBD's effect on minimal muscular and neurologic impairment using a rotor rod test where they reported CBD treatment was well-tolerated in both mice and rats. Another recent study observed both additive and antagonistic effects of CBD when combined with other AEDs. A significant synergistic interaction was found between levetiracetam and CBD at a 1:1 fixed ratio, clobazam and carbamazepine both produced antagonistic interactions at a 1:3 fixed ratio (Smith et al., 2015).

A succession of experiments examined the effects of THC and CBD for controlling seizures in different animal models of epilepsy (Wallace et al., 2001, Wallace et al., 2002, Wallace et al., 2003). Both THC and CBD produced anticonvulsant effects in rodents (Wallace et al., 2001). Akin to phytocannabinoids, the endogenous cannabinoid, anandamide, produced an anticonvulsant effect (Wallace et al., 2002). Moreover, certain cannabinoid receptor antagonists cause status epilepticus-like pro-seizure activity (Deshpande et al., 2007). Experimental studies linked the CB₁ receptors to the anticonvulsant activity of THC, but did not mention the mechanistic aspects of CBD. A variety of mechanisms are linked to CBD protective effects which are described in the next sections (Consroe et al., 1982; Jones et al., 2010; Patel et al., 2014). Overall, there is strong evidence indicating the anticonvulsant activity of CBD compounds (Wallace et al., 2001; Blair et al., 2015), but the exact neuronal mechanisms are unclear. This is further elaborated in the next subsection.

In addition to the preclinical CBD trials, investigations of the synergistic interactions and additive effects of CB₁ receptor agonists and standard antiepileptic drugs have been conducted. WIN55212, a CB₁ receptor agonist with similar effects to THC, has been at given at low doses in tandem with low doses of ethosuximide (Luszczki et al., 2011a), phenobarbital (Luszczki et al.,

2011a; Luszczycki et al., 2011b), valproate (Luszczycki et al., 2011a; Luszczycki et al., 2011b), carbamazepine (Luszczycki et al., 2011b), phenytoin (Luszczycki et al., 2011b), and diazepam (Naderi et al., 2008) to produce enhanced anticonvulsant effects in mice. In a similar fashion, the synthetic CB₁ receptor agonist, arachidonyl-2'-chloroethylamide (ACEA), was tested with low dose injections of naltrexone (Bahremand et al., 2008) and phenobarbital (Luszczycki et al., 2009) to produce an additive anticonvulsant effect in mice. It is important to be noted, however, that there is evidence suggesting that WIN55212 not only enhances the anti-seizure effects of common antiepileptic medications such as carbamazepine, phenytoin, phenobarbital, valproate and ethosuximide in mice, but also the negative side-effects of these drugs, i.e. the impairment of motor co-ordination, as well as the impairment of long-term memory by phenytoin, phenobarbital, valproate and ethosuximide (Luszczycki et al., 2011a; Luszczycki et al., 2011b; Pertwee, 2012). This contrasts the actions of the CB₁ selective agonist, ACEA, which enhance the anticonvulsant effects of phenobarbital without changing the impairment on motor co-ordination, long-term memory or skeletal muscle strength generally seen with this barbiturate (Luszczycki et al., 2009). The cerebellum and neocortex are two regions of the brain that are involved in the initiation and coordination of movement. Humans express a higher proportion of CB₁ in the limbic system and cerebral cortex, and have lower expression in the cerebellum than rats, which may illuminate the suggestion that motor function more compromised in rodents when they are administered cannabinoids (Pertwee, 2008).

Clinical Studies

In contrast to a great deal of preclinical data, supportive clinical data is rather limited. Much of the information concerning the clinical effects of marijuana in human patients has been either anecdotal or survey material. At present, 19 small trials are underway to study whether non-psychoactive cannabinoids may be useful as antiepileptics (ClinicalTrials.gov). Table 2 provides a summary of various clinical studies of cannabis or CBD products in epilepsy.

A Cochrane systematic review was conducted over the use of CBD enriched therapies for the treatment of epilepsy (Gloss and Vickery, 2014). This Cochrane review searched for randomized, controlled clinical trials that show direct evidence of the anticonvulsant effects of medical marijuana or CBD in human seizures. They identified only four studies that fit their efficacy criteria, with a total sample of 48 participants in clinical studies, randomized to placebo or to 200–300 mg of CBD per day (Mechoulam and Carlini, 1978; Cunha et al., 1980; Ames and Cridland, 1985; Trembly, 1990). In general, short-term tolerability of CBD-enriched therapeutics was demonstrated in these studies, only

noting minor side effects such as drowsiness. However, with the exception of a single study which had reported 2/4 patients treated with CBD becoming seizure free for 12 weeks, the experiments reported either no benefit, or the effect of treatment was not clearly stated.

There are several additional studies and more recent clinical studies which have investigated the effect of CBD on epilepsy patients. Two case studies that received a lot of media attention reported patients who became seizure free when treated with medical marijuana or extracts of its components (Eisenstein, 2015). In one case, a 24 year old man self-treated with 2-5 joints per night in addition to his prescribed anti-epileptic medications and experienced a reduction in seizures (Consore et al., 1975). The second case, which convinced many parents with epileptic children to move to Colorado, featured a young girl named Charlotte who had been diagnosed with severe Dravet Syndrome. After she was started on a low dose of a sublingual preparation of a cannabis extract in tandem with her prescribed clobazam, Charlotte experienced a >90% decrease in seizures by the third month of treatment. This strain of marijuana has a 16:1 ratio of CBD to THC, and is now referred to as “Charlotte’s Web” because of the success Charlotte had found using the extract (Maa and Figi, 2014). A case series in 1949 indicated that 2/5 institutionalized children with mental retardation and refractory epilepsy had achieved a significant decrease in seizure activity when treated with a homolog of THC (Davis and Ramsey, 1949).

Several patient or caregiver surveys have been performed examining the effects of CBD or CBD-enriched products in epilepsy. In one survey, 16/19 responders reported a reduction in seizure frequency while taking medical marijuana. Some responders also noted other beneficial effects such as improved sleep and mood (Porter and Jacobson, 2013). Another survey reported 8/11 responders had experienced an almost 100% reduction in seizure activity when taking Realm Oil, an extract of Charlotte’s Web, as a therapeutic option (Gedde and Maa, 2013). Furthermore, 75 patients or caregivers who had started taking oral cannabis extracts for refractory epilepsy were asked about their perceived efficacy of the products. Of the responders, 57% reported improvement to either seizure duration or frequency. The responder rate varied based on the type of epilepsy: Dravet 23%, Doose 0%, and Lennox-Gastaut syndrome 89%. However, there was a discrepancy in responder rate between patients with preexisting residency in Colorado and those patients who had moved to Colorado seeking oral cannabis treatments, finding that those patients who had moved to Colorado were more than 3 times as likely to report a >50% seizure reduction than those who had a preexisting residency (Press et al., 2015). In a press release, GW Pharma reported results on both efficacy and

safety data on patients who received Epidiolex (> 97% CBD, < 3% THC) as part of their daily regimen for at least 12 weeks. Data from 58 patients was reported from those suffering from a range of treatment-resistant epilepsies including Dravet syndrome. The median reduction in seizure frequency was 43% for all patients. The most frequently stated side effects included fatigue and somnolence; however, diarrhea and changes in appetite were also observed, with ~80% of patients reporting at least one side effect.

Few prospective trials have been conducted that involve the use of isolated cannabinoids as a therapeutic option for epilepsy. As mentioned previously, the Gloss and Vickrey Cochrane study found only 4 placebo-controlled studies using CBD as a treatment for epilepsy. In all four studies, patients with uncontrolled seizures were randomized into either placebo or CBD groups. The patients in the experimental groups were given between 200-300 mg of CBD. Of the four studies, two had reported a difference in seizure frequency between the two groups (Cunha et al., 1980; Mechoulam and Carlini, 1978) whereas the remaining two studies provided few details but suggested little or no difference in seizure frequency between placebo and CBD groups (Ames and Cridland, 1985; Trembly, 1990). Recently, there has been a surge in clinical trials investigating the additive effects of CBD to daily AED regimens in both children and adults. In 2014, a prospective observational study reported 9/23 patients experienced above a 50% decrease in seizures, with a median reduction in seizures of 32% for all patients when treated with 25 mg/kg/day of Epidiolex in tandem with prescribed AEDs (Devinsky et al., 2014b). Similar reports were made in a 2015 study with 25 patients (Oldham et al., 2015). In addition to these trials, two additional studies were performed investigating drug-drug interactions between CBD products frequently prescribed AEDs. Both studies found a change in serum levels when CBD products and clobazam were taken in tandem (Friedman et al., 2014; Geffrey et al., 2015). For those patients, the dose of clobazam was reduced. A 50-55% decrease in seizures was experienced in 11/13 patients; however, the remaining 2/13 had an increase in seizure activity (Geffrey et al., 2014). In all the human trials, no major adverse effects were mentioned; however, minor side effects included somnolence, fatigue, diarrhea, and changes in appetite.

Recently, a survey was performed in Alabama discussing relationships between socioeconomic status and admission into CBD oil epilepsy trials and found that the recipients were racially/ethnically monolithic (white) and typically in higher-income groups with private medical insurance (Hansen et al., 2015). This contrasts the relatively low-income, high proportion of African

American population in this region and clearly documents a disadvantage for these people with epilepsy and in need of care. The American Epilepsy Society (AES) has released a statement on the use of medical marijuana in the treatment of epilepsy stating that due to the lack of data, no conclusion can be drawn at present; however, the AES supports well-controlled studies that will lead to a better understanding of epilepsy and the effects cannabinoids might have in the development of safe and effective treatment options for those affected by the disease. All of studies mentioned involved epileptic patients, both children and adults, with varying forms of refractory epilepsy and report moderate seizure reduction with only mild side effects. Furthermore, due to the lack of conclusive data, fewer epilepsy specialists support prescribing CBD products and medical marijuana to their patients compared to other medical professionals or recipients of these therapeutics, according to a survey conducted by *Epilepsia* (Mathern et al., 2015).

In essence, these studies also reveal tolerability, safety and drug interactions with cannabis use. CBD is well tolerated in humans with doses up to 600 mg without resulting in severe reactions or psychotic symptoms (Table 2). No significant CNS effects were noted in the few small placebo-controlled studies performed. However, when CBD is taken orally, it first undergoes an extensive first-pass metabolism with low bioavailability (~6%). The half-life of CBD, when administered this way in humans, is approximately 1 to 2 days. CBD is a powerful inhibitor of many CYP isozymes, including CYP 2C and CYP3A, indicating a potential for drug-drug interactions when taken with other medications.

One of the most serious concerns of cannabinoid therapeutics is their potential for abuse. Cannabinoids have been proposed to modify reward mechanisms (Gardner and Vorel, 1998) and as most abused drugs, they can increase dopamine release to the nucleus accumbens (NAC) (Tanda et al., 1997). However, synthetic cannabinoids (WIN55212-2 and CP55940) were not able to increase dopamine levels within acute NAC slice preparations, nor were CB₁ receptors particularly dense in the ventral tegmental area where the mesolimbic dopaminergic pathway originates (Szabo et al., 1999; Mailleux and Vanderhaeghen, 1992; Tsou et al., 1998). This data indicates that the forebrain regions that project to the NAC may be indirectly involved with the elevation of dopamine. Furthermore, glutamatergic neurons in the BLA increase their activity when rewarding stimuli is presented (Muramoto et al., 1993). It is suggested that cannabinoids modulate the dopaminergic pathways by reducing the tonic GABAergic inhibitory control over pyramidal cells in the basolateral

complex of the amygdala (Katona et al., 2001). Preclinical and clinical investigations on the safety and efficacy of these products continue to be pursued for more conclusive answer to these concerns.

Pharmacological Basis of Cannabis Use in Epilepsy

Despite such widespread therapeutic interest in cannabis, the mechanistic rationale for cannabis use in epilepsy remains an enigma. The pharmacological mechanisms underlying such therapeutic claims for epileptic seizures are poorly understood. At the systems level, it is likely that CBD or related constituents in the cannabis can affect the endocannabinoid system and thereby modulate neural networks involved in generation or spread of hyperexcitability and epileptic seizures. In this context, the specificity and non-specificity of CNS actions of cannabis is an important aspect for epilepsy therapeutics. This distinction between specific and non-specific drug mechanisms is often difficult to define in the case of cannabis use or even with CBD-predominant products, mostly due to limited data on the dose-response relationship of the drug for the intended therapeutic efficacy. The therapeutic dynamics become even more complex if the drug has a broad spectrum of targets, which can result in unpredictable activity if the drug product contains multiple active compounds or is not produced based on standard manufacturing practices. Although control of epileptic seizures is the goal when administering a cannabis product, it is possible to cause unintended side effects likely resulting from its potential off-target effects.

Endocannabinoid System

The primary pharmacological effects of cannabinoids occur due to its interaction with cannabinoid (CB) receptors in the CNS and also in the periphery. The presence of cannabinoid receptors type 1 and 2 (CB₁/CB₂) in the brain initiated the investigation and discovery of endogenous cannabinoids such as anandamide and 2-arachidonylglycerol, which are ligands for CB_{1/2} receptors (Koppel, 2014). The name “anandamide” is derived from the Indian Sanskrit word “anand” for bliss or happiness and the suffix “-amide”. Anandamide is related to CBD and shares some of the same molecular targets. Cannabinoid receptors are ubiquitous throughout the CNS, and are often co-expressed to presynaptic G_i protein-coupled receptors (Hofmann and Frazier, 2013). Both CB₁ and CB₂ receptors are linked to G_i and inhibition of adenylyl cyclase activity. Activation of CB₁ receptors result in inhibition of glutamate release. The two primary natural endogenous ligands for these receptors are the arachidonic acid derivatives anandamide (N-arachidonoyl-ethanolamine) and 2-arachidonoyl glycerol (2-AG) (Maa and Figi, 2014; Devane et al., 1992). The strong lipophilic nature

of cannabinoids provides for efficient targeting of intracellular sites, stimulating increases in intracellular calcium concentrations in a wide range of neuronal cell types. Endocannabinoid activity has also been observed in a significant number of immune cells types, including (but not limited to): basophils, dendritic cells, lymphocytes, macrophages, and monocytes (Matias et al., 2002). Anandamide and 2-AG are rapidly hydrolyzed by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (Dinh et al., 2002a; Dinh et al., 2002b; Nomura et al., 2011). Anandamide and 2-AG have been identified around both GABAergic and glutamatergic neurons involved in regulating excitability and seizure susceptibility, which may explain some of the anticonvulsant properties of these molecules (Maa and Figi, 2014).

The two types of endocannabinoid receptors share 44% amino acid homology, have seven transmembrane domains, and are associated with G_i protein-coupled receptors, linking them to signaling cascades within the cell (Munro et al., 1993). Both the CB₁ and CB₂ receptors are activated by the endocannabinoids anandamide and 2-AG. The CB₁ receptor is expressed pre-synaptically on both glutamatergic and GABAergic interneurons throughout the CNS as well as throughout the periphery (Gerard et al., 1991). It is principally accountable for the psychoactive effects associated with THC, and stimulation of this receptor also plays a role in regulating stress responses, pain, lipogenesis, and energy regulation. In contrast, the CB₂ receptors are predominantly expressed throughout the immune system, though are sparsely expressed within the CNS as well, generally located on microglial cells (Cabral et al., 2015). The complexity of the endocannabinoid system throughout the CNS and the periphery may offer various targets to modulate the endocannabinoid signaling (Hill et al., 2010; Hering et al., 2011; Naderi et al., 2015; Iannotti et al., 2014). There is also evidence of dysfunction in the endocannabinoid systems in epilepsy. Patients who were newly diagnosed with temporal lobe epilepsy were identified to have significantly lower levels of anandamide in cerebrospinal fluid when compared to healthy counterparts (Romigi et al., 2010; Ludányi et al., 2008).

Δ⁹-Tetrahydrocannabinol

THC is the most abundant compound found in cannabis. THC is believed to be responsible for the psychoactive effects commonly associated with smoking marijuana and is therefore associated with many of the diverse effects marijuana including changes in human cognition and perception (Hofmann and Frazier, 2013). THC acts as a partial agonist of CB₁ receptors, which are found primarily in the CNS, as well as on CB₂ receptors located primarily on the cells of the immune

system. There is some discrepancy in the investigation of the anticonvulsant effects of THC. Much of the research suggests that THC produces anti-convulsant effects and could therefore be a potential constituent in epilepsy therapeutics (Wallace et al., 2001; Consroe et al., 1982). The mechanism by which THC produces these anticonvulsant effects is suggested to be through the CB1 receptors (Detyniecki and Hirsch, 2015). There are also few conflicting studies that show no decrease in seizure activity and, in some cases, was found to elicit more frequent seizures (Devinsky et al., 2014a; Karler et al., 1984; Santos et al., 2014). The potential for tolerance and the psychoactive effects of THC could be critical limiting factors for advancing the clinical potential of THC.

Cannabidiol

CBD, a major phytocannabinoid found in cannabis, accounts for up to 40% of the plants extract (Campos, 2012). Due to its lack of psychoactive properties and low rate at which a tolerance develops, CBD is considered to have a much wider therapeutic potential for epilepsy when compared to THC. CBD has anticonvulsant (Devinsky et al., 2014a; Consroe et al., 1982, Martin et al., 1987), anti-inflammatory (Li et al., 2013; Malfait et al., 2000) and anti-tumorigenic activities (McAllister et al., 2011). Although CBD has a low affinity for both the CB₁ and CB₂ receptors, at high levels, it can act as an indirect CB₁ antagonist, and has been shown to affect the threshold of seizures in some animal studies (Wallace et al., 2003). In addition, CBD is known to down-regulate FAAH and 5-lipoxygenase enzymes (Capasso et al., 2008), inhibit the uptake of adenosine (Liou et al., 2008), bind to both transient receptor potential vanilloid 1 (TRPV) (Iannotti et al., 2014) and 5-HT_{1-2A} receptors (Russo et al., 2005). This affinity for the 5-HT_{1A} and 5HT_{2A} receptors may provide a novel target for refractory epilepsy. The 5HT_{1-2A} receptors are known to act as a target for fenfluramine, a drug that has seen some effectiveness for Dravet syndrome (Ceulemans et al., 2012). A limited number of investigations have reported changes in 5-HT receptor function or expression in epileptic patients; however, it remains uncertain whether this is a cause of the disease or a factor of epileptogenesis (Bih et al., 2015; Theodore et al., 2007). In addition, CBD may also exert antioxidant effects (Hampson et al., 1998). Therefore, when CBD products are administered, it can be difficult to unambiguously distinguish between effects of, for example, cannabinoid receptor- and non-cannabinoid-mediated actions, which is an important consideration when investigating new therapeutic options.

Cannabidivarin (CBDV) is a propyl analogue of CBD (Vollner et al., 1969). CBDV also elicits anticonvulsant effects in animal models (Hill et al., 2012). There is limited knowledge about

the mechanisms of CBDV, although it is reported that CBDV acts via the CB₂ receptors and other targets (Scutt and Williamson, 2007; Iannotti et al., 2014).

Cannabinoid CB₁ Receptors

CB₁ receptors are widely expressed throughout the CNS, specifically located within the basal ganglia, cerebellum and neocortex, spinal cord, hippocampus and amygdala. The CB₁ receptors are found on axonal terminals near the release sites of the presynaptic neuron and reduce neurotransmitter release (Alger, 2014). The influence on both excitatory and inhibitory synapses leads to potentially complex outcomes. The CB₁ receptors expressed within in the basal ganglia are responsible for the well documented effects on locomotor activity in rodents (Veeraraghavan and Nistri, 2015; Lee et al., 2006; Bosier et al., 2010). As in other areas of the brain, these receptors inhibit the release of both glutamate and GABA, depending on the type of neuron expressing the receptor. Thus, CB₁ activation inhibits both excitation and inhibition in a dose-dependent triphasic pattern. Locomotor activity is decreased with both high and low doses, whereas, moderate doses were shown to heighten motor activity in rodents (Elphick, 2001).

CB₁ receptors in the spine, particularly those on interneurons in the dorsal horn, are responsible for much of the documented analgesic effects of cannabis. Layers 1 and 2 of the dorsal horn, which target a variety of peripheral nociceptive terminals, contain the heaviest expression of CB₁ receptors (Hoheisel et al., 2011). It is thought that endogenous cannabinoids exert an analgesic effect through these receptors (Elphick, 2001).

CB₁ receptors are densely located on the glutamate-releasing pyramidal cells of the cornu ammonis (CA1-3) within the hippocampus, one of the major regions of the brain affected by epilepsy. By inhibiting the release of glutamate, these receptors indirectly block NMDA-modulated excitatory currents, and therefore suppress the initiation of learning-memory related phenomenon of long-term potentiation and long-term depression (Baron, 2015; Goodman and Packard, 2015). The expression of CB₁ receptors in the rat hippocampus underwent a strong, plastic response following status epilepticus (Falenski et al., 2009). The basolateral complex exhibited heavy expression of CB₁ receptors, while in other areas such as the central nucleus there is little expression of CB₁ receptors (Katona et al., 2001).

Two important studies have increased the understanding of the endocannabinoid system showing that it is promptly activated following seizure activity. The first showed that blocking the CB₁ receptor in epileptic rats led to an increase in both seizure frequency and duration (Wallace et al.,

2003). This study signified that CB₁ activation is a response to seizure activity, rather than a cause, since this response was not elicited in control rats. In support of this insight, the researchers found the level of 2-AG increased in the hippocampus within 15 minutes after a single pilocarpine-induced seizure. Another study demonstrated glutamatergic neurons in the forebrain are predominately responsible for the cannabinoid-mediated protection against seizures (Marsicano et al., 2003).

Cannabinoid CB₂ Receptors

CB₂ receptors are found predominantly in the peripheral tissues of the immune system where they are primarily responsible for mediating the release of cytokines (Galiègue et al. 1995, Pertwee, 2006). CB₂ receptors are localized on immune cells such as monocytes, B-cells, T-cells and macrophages (Galiègue et al. 1995; Basu et al., 2011; Ashton and Glass, 2007). CB₂ receptors are also expressed in the brain, though not as densely as CB₁ receptors. Interestingly, the CB₂ receptor is found primarily on microglia and not on neurons, unlike the CB₁ receptor (Pertwee, 2006). Consequently, specific CB₂ agonists are suggested as possible therapeutic targets for treatment of inflammation and pain, especially neuropathic pain. A study revealed that synthetic cannabinoid agonists of CB₂ receptors exhibit changes in cAMP levels, causing inhibition of T cell signaling (Cheng and Hitchcock, 2007). The CB₂ agonist JWH-015 was found to activate macrophages in order to remove β -amyloid protein from frozen human tissues (Tolón, 2009). This evidence suggests that CB₂ receptors may also hold therapeutic potential for neurodegenerative diseases such as Alzheimer's disease.

Conclusions and Perspectives

Cannabinoids are used to treat a variety of nervous system conditions (Wissel et al., 2006; Notcutt, 2015). There are many ongoing trials on a diverse range of cannabinoids that have been shown to be beneficial for epilepsy (Wallace et al., 2001; Cunha, 1980); however, there have also been studies that show that cannabis can have variable effects on seizures in different species (Meldrum et al., 1974; Martin and Consroe, 1976; Chiu et al., 1979). Preliminary evidence reveals therapeutic potential for cannabinoids, particularly CBD, to reduce seizure frequency and duration. In patient or care-giver surveys, the majority of responders claimed to observe beneficial effects or no significant effects of cannabis in epileptic children. Bulk of the data suggests that cannabinoids exert at least partial protection in patients with rare forms of epilepsy, such as Dravet syndrome and Lennox-Gastaut syndrome. Many of the clinical trials administered cannabis in tandem with the

patient's previously prescribed medications. Some of those patients were able to lower the dosage of those medications, and in some cases completely stop their previous medication, with no increase in seizures during the trial period.

Although cannabis has been used medicinally for centuries, it is only within the last few decades that our understanding of the mechanisms of the cannabinoid system and the potential benefit of these mechanisms has begun to accumulate. Cannabinoids have anticonvulsant effects in animals. It is well known that they can exert a variety of effects in the CNS and the periphery. Their main target is the endocannabinoid system, which is involved in regulating neurotransmitter networks and other peripheral functions. This occurs through CB₁ receptors which are principally distributed throughout the brain and through the CB₂ receptors that are preferential to the peripheral and immune tissues. Amid dozens of cannabinoids found in cannabis, so far two show medicinal promise. The first, THC (controlled substance), is the CB₁ agonist that has potent anticonvulsant and psychoactive properties. The second, CBD (non-controlled substance), acting on CB₂, lacks psychoactivity, but modulates seizures and immune function. THC is a potent antiepileptic in both animals and humans; however the relatively high rate of tolerance development and psychoactive properties diminish its therapeutic potential. CBD has also been shown to elicit anticonvulsant and anti-inflammatory effects in several studies. Although CBD has a low affinity for the CB₁ and CB₂ receptors, the exact mechanism by which this agent affects seizures remains unclear and perhaps involves more complex systems (Brodie et al., 2015).

There are potential side effects of cannabis use that include psychiatric, sleep, and cognitive impairments. Marijuana use is not always thought of as an appropriate therapeutic option. Apart from THC, there are other cannabinoids found within marijuana that have psychoactive properties and would thus be undesirable for therapeutics. New studies on cannabis use yield some insight on safety issues. Two recent studies explored the effect of cannabis on subcortical brain structures and brain maturation in adolescence in relation to risk of schizophrenia. Pagliaccio and colleagues (2015) analyzed the effects of cannabis use in a large sample (n=483) of twins and siblings enrolled in the Human Connectome Project, 262 of which who reported using cannabis in their lifetime. Smaller left amygdala and right ventral striatum volumes were found in those participants who reported cannabis use, though differences were within the range of normal variation. French and colleagues (2015) found that cannabis use might affect the maturation of the cerebral cortex in adolescents with risk of

schizophrenia by means of their respective polygenic risk score. These types of studies provide indications on the general safety in exposing young people to cannabis (Goldman, 2015).

As of December 2015, there are 19 clinical trials in progress that have been evaluating CBD for epilepsy (see, clinicaltrials.gov). Given the growing interest and clinical data, professional medical establishments began formulating guidelines about cannabis use for epilepsy. In 2014, the AES, the leading organization of clinical and research professionals in epilepsy, has released a position statement on medical marijuana (www.aesnet.org/about_aes/position_statements). The essence of this statement include (a) Positive effects of the CBD are from anecdotal reports only with robust scientific evidence lacking to establish medical marijuana as a safe and effective treatment for epilepsy; (b) Potential negative effects on learning, memory, and behavior; (c) Should be studied using well-founded research methods; (d) Status as a Schedule 1 substance should be reviewed; and (e) The risk/benefit ratio does not currently support the use of marijuana for treatment of seizures at this time. Despite all of the controversial challenges of medical marijuana as a potential therapy for epilepsy, what is not disputed is the need for scientific investigation into cannabinoids to prove or disprove their safety and efficacy for epilepsy therapy. Since the mechanism of CBD's seizure protection is unknown, identification of mechanisms driving anticonvulsant efficacy are additionally critical for helping to identify other potential treatment options.

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Wrote or contributed to the writing of the manuscript: Doodipala Samba Reddy, Victoria M. Golub

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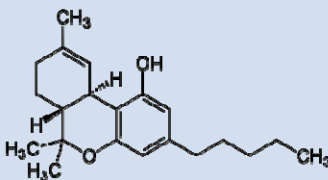
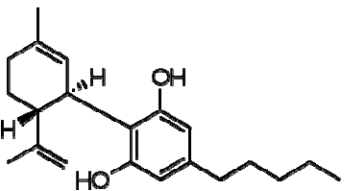
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Footnote:

The opinions and assertions contained herein are the private views of the coauthors and do not represent the official position or policies of the Texas A&M Health Sciences Center, The Texas A&M University system, or the Texas Government.

Table 1. Comparative pharmacology of the cannabinoids THC and CBD.

Cannabinoid type	Chemical structure	Pharmacological actions	Potential Targets	References
Δ^9 - Tetrahydrocannabinol (Δ^9 -THC)		Anticonvulsant Euphoria Psychoactive Analgesic Cognitive modulation Reduces muscle spasms Reduces nausea Stimulates appetite	CB ₁ partial agonist CB ₂ partial agonist TRPA1 agonist TRPV2 agonist TRPM8 antagonist $\alpha_1\beta$ Gly enhancer 5-HT _{3A} antagonist PPAR- γ activator GPR18 agonist GPR55 agonist	<i>Cascio and Pertwee, 2014;</i> <i>Pertwee and Cascio, 2014;</i> <i>Friedman and Devinsky, 2015</i> <i>Blair et al., 2015</i>
Cannabidiol (CBD)		Anticonvulsant Analgesic Anti-inflammatory Anti-tumorigenic Neuroprotective Reduces nausea Immune modulation	CB ₁ ligand CB ₂ ligand TRPA1 agonist TRPV1-3 agonist TRPV4 agonist TRPM8 antagonist 5-HT _{3A} antagonist α_3 Gly enhancer GPR55 antagonist 5-HT _{1A} enhancer PPAR- γ activator Adenosine reuptake inhibitor	<i>Cascio and Pertwee, 2014;</i> <i>Pertwee and Cascio, 2014;</i> <i>Friedman and Devinsky, 2015</i> <i>Blair et al., 2015</i>

Several cannabinoids are known to bind to multiple targets in the CNS and exert effects at low micromolar and nanomolar concentrations. Both Δ^9 -THC and CBD have shown anticonvulsant effects in preclinical models of epilepsy, as well as producing other actions such as acting as an anti-inflammatory or neuroprotective agent. The non-specific actions of cannabinoids present a potential issue as a therapeutic option, as many questions about the safety and efficacy of these compounds remain elusive.

Table 2. Chronological summary of clinical reports and surveys on the use of cannabinoids for epilepsy (1949-2015).

Reference	Study	Subjects	Study Details	Results	Adverse Effects
Davis and Ramsey, 1949	Case series of 5 institutionalized children with mental retardation and epilepsy	5	Treated for 10 weeks with two isomeric-3 homologs of THC	3 patients responded at least as well to their previous AEDs, the remaining 2 had significant decrease in seizures	None reported
Consroe et al., 1975	Case study of a 24-year old male with refractory epilepsy	1	Patient would self-treat with 2-5 joints per night while continuing to take prescribed medications	Nearly seizure free with daily marijuana use in tandem with prescribed AEDs	None reported; patient was not able to completely control seizures on marijuana alone
Mechoulam and Carlini, 1978	Placebo-controlled trial in epileptic patients	9 total; 4 treatment, 5 placebo	Treated with 200 mg of CBD in tandem with prescriptions for 3 months	2/4 treatment group were seizure-free for the duration of the study; 0/5 placebo group had seizure improvement	None reported
Cunha et al., 1980	Placebo-controlled trial in teenagers and adults with TLE	15 total; 8 treatment, 7 placebo	Treated with 200-300 mg CBD or placebo per day for up to 4.5 months	4/8 were seizure-free for the duration of the study; 3 others showed partial improvement	Somnolence in some participants
Ames and Cridland, 1986	Placebo-controlled trial in patients with uncontrolled seizures	12 total; 6 treatment, 6 placebo	Treated with 200-300 mg CBD or placebo per day for 1 month	Little difference was reported between the treatment and placebo groups, although not much detail was given	Somnolence was reported as a side effect for some participants
Gedde and Maa, 2013	Survey of parents of pediatric epilepsy patients who had been taking Realm Oil as a therapeutic option. Diagnoses included Doose, Dravet and Lennox-Gastaut as well as other refractory epilepsies	11	Realm oil (extract of 16:1 CBD cannabis plant) was given as a therapeutic option for at least 3 months. Average dose was between 4-12 mg/kg/day.	11/11 patients experienced a reduction in weekly motor type seizure frequency; 8/11 experienced almost 100% reduction; 1/11 had a 75% reduction; 2 reported 20-45% reduction	Sedation and unsteadiness
Porter and Jacobson, 2013	Survey was conducted on parents who had children with epilepsy who were currently using CBD-enriched cannabis products	19	Parents of pediatric epilepsy patients were surveyed on their children's seizure frequency and duration	16/19 responders reported a reduction in seizure frequency while taking medical marijuana; others reported beneficial effects like improved sleep and mood	Drowsiness and fatigue were reported by some parents
Devinsky et al., 2014b	Prospective observational study including both children and adults with treatment-resistant epilepsies where CBD treatment was added to their daily AED regimen	23	Epidiolex (98% CBD oil) was given to patients for 3 months in tandem with previous prescriptions at a maximum dose of 25 mg/kg/day	9/23 patients experienced >50% reduction in seizures; median reduction in seizures 32% for all patients; 1/23 had increased seizure activity	Somnolence and fatigue
Friedman et al., 2014	Drug-drug interaction trial between Epidiolex (CBD) and clobazam in epileptic patients	33 total; 17 CBD treatment, 16 clobazam control	Treated with CBD 25 mg/kg/day in tandem with clobazam	A median change in AED serum levels was found for clobazam of 8.3%. 7/17 patients taking clobazam required a clobazam dose reduction due to a drug-drug interaction	None reported

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GW Pharma, 2014	Press release providing safety and efficacy data for Epidiolex treatment trials	58	Epidiolex (98% CBD oil) was given to patients for at least 12 weeks in tandem with their previous prescriptions	Median reduction in seizure frequency was 43% for all patients	Fatigue, somnolence, diarrhea and changes in appetite were observed in some patients
Maa and Figi, 2014	Case study of a 5-year old female with severe Dravet syndrome	1	Patient was given low dosage of sublingual preparation of low THC, high CBD marijuana extract daily	>90% decrease in total seizures after 3 months of treatment; Patient was able to wean off of previously prescribed medication	None reported
Geffrey et al., 2015	Drug-drug interaction trial between CBD and clobazam in patients with refractory epilepsy	25 total; 13 CBD treatment, 12 clobazam control	Treated with CBD 25 mg/kg/day in tandem with prescribed clobazam for 4 weeks	11/13 patients experienced a 50-55% decrease in seizure activity; 2/13 patients had an increase in seizure activity	Drowsiness, ataxia and irritability were observed in some patients
Hansen et al., 2015	Survey conducted at University of Alabama at Birmingham and Children's of AL medical centers on the relationship between socioeconomic status and recipients of CBD oil epilepsy trials	23	Questions asked on household income, level of education, and medical insurance	Racially/ethnically monolithic (white) Majority pediatric (52.2%) Majority female (62.2%) Private health insurance (65.2%) Medicaid or state insurance (26.1%) Household income >50-60K (70%) Household income >100K (28.6%) "Special education until 21 program" (72.7% adults)	N/A
Oldham et al., 2015	Observational study of children and adolescents who received Epidiolex as an addition to their daily AED regimen	25	Participants were treated with up to 25mg/kg/day of Epidiolex (98% CBD oil) for up to 12 months. Baselines were checked at 3 months and 12 months.	3 Months: 32% of patients had a above 50% seizure reduction 12 Months: 40% of patients (10) had above 50% seizure reduction	Food aversion, diarrhea, changes in diet or weight loss
Press et al., 2015	Retrospective survey on pediatric patients with varying types of epilepsy who were taking oral cannabis extracts	75	Survey conducted on seizure frequency and duration	57% of responders reported improvement of seizure duration and frequency	None reported