Cannabidiol has Anticonvulsant Effects: A Narrative Review

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Abstract

Epilepsy is a chronic neurological disorder characterized by recurrent seizures. Cannabidiol's anticonvulsant effects have been widely recognized since the 1980s, however the possible mechanisms of action have continued to grow throughout preclinical research. Cannabidiol is a multitarget drug, meaning it may simultaneously target numerous enzymes and receptors to produce anticonvulsant effects. Cannabidiol inhibits anandamide degradation so that anandamide may also produce effects through additional targets. Because there are multiple possible direct and indirect targets for cannabidiol to produce anticonvulsant effects, the exact mechanism of action is unknown. This narrative review describes physiological commonalities between epileptic patients and possible anticonvulsant targets of cannabidiol based on those commonalities.

Introduction

Antiepileptic drugs are used to prevent cell damage/death after a seizure occurs and prevent physiological changes that promote later seizures. Unfortunately, some epileptic patients are resistant to antiepileptic drugs. Research suggests that cannabidiol (CBD) is an effective alternative to antiepileptic drugs [1,2,3,4]. Before most of CBD's medicinal properties were discovered, CBD was recognized for its anticonvulsant effects [5]. Preclinical and clinical trials repeatedly show anticonvulsant effects of CBD, including normalizing intracellular Ca^{2+}, reducing neuroinflammation, and reducing oxidative stress [1,2,6,7,8]. These characteristics suppress the maintenance and progression of epilepsy [1].

Murine models of epilepsy have allowed researchers to test the safety and efficacy of CBD. In 2017, CBD treatment was given to rats before pilocarpine-induced seizure (2 hour seizure) [2]. They found that CBD treatment not only prevents physiological changes after an epileptic seizure, but reduces behavioral and oscillatory electrographic power during an epileptic seizure. This means, CBD treatment suppresses the severity of seizures and reduces neuron damage/death after the seizure [2]. Another study showed the effects of CBD treatment on

pentylenetetrazole-induced seizure in mice [3]. Results showed that pretreatment of CBD attenuated seizures and electrical activity of the brain associated with seizures [3].

Human studies confirm the safety and efficacy of CBD treatment for epilepsy. As early as 1980 human studies showed the anticonvulsant effects of CBD [5]. A prospective double-blind study by Cunha et al. showed 8 epileptic patients resistant to antiepileptic drugs. After 30 days of CBD treatment, 4 remained almost free of epileptic seizures, 3 demonstrated partial improvement, and 1 showed no signs of improvement. These results were compared to a placebo group, who showed no signs of improvement [5]. A 2016 study showed the effects of CBD treatment on 74 pediatric epileptic patients resistant to antiepileptic drugs. Results showed CBD treatment effectively reducing seizure frequency in 89% of patients. In addition, researchers observed improvement in behavior, alertness, language, communication, motor skills and sleep [9].

Many other studies confirm CBD's anticonvulsant effects, however CBD's mechanisms of action to achieve anticonvulsant effects is still unclear. To understand CBD's possible targets, this review will discuss physiological commonalities between epileptic patients. In addition, this review will discuss possible mechanisms of action based on those commonalities between epileptic patients.

A. Commonalities in Epilepsy

Epilepsy is a chronic neurological disorder characterized by recurrent seizures and the physiological, cognitive, behavioral, and social changes associated with the seizures [2,10]. By definition, epilepsy is a condition resulting from failure of the mechanisms responsible for seizure termination or dysfunctional mechanisms leading to prolonged seizures [10]. In essence, epilepsy is defined by epitogenesis, seizure-induced pathological changes that promote later seizures. Epitogenesis includes altered gene expression, inflammation, protein production and changes in neuronal signaling [10,11]. Though the exact etiology of epilepsy is unclear, the following will describe commonalities between epileptic patients that give insight to therapeutic targets in epilepsy treatment.

During a seizure, normal neuronal signaling goes haywire [12]. After the seizure, a major commonality between epileptic patients is an altered glutamatergic transmission system, an essential factor of epitogenesis [13,14]. The glutamatergic transmission system plays an important role in the formation of neuronal networks and synaptic plasticity, therefore regulation of glutamate transmission is critical in maintaining neuronal homeostasis [13,11]. In simpler terms, too little or too much glutamate release has harmful neurological effects. In a healthy brain, glutamate transmission is modulated by Ca^{2+} channels on presynaptic neurons, in that increased Ca^{2+} permeability facilitates the presynaptic release of glutamate [11]. Once glutamate is released, it activates glutamate receptors on specific cells of the nervous system to relay chemical messages. After glutamate is used to relay chemical messages, it is transported to its degradation by glutamate uptake transporters.

After a seizure, the brain decreases the expression of glutamate uptake transporters [12], causing an accumulation of glutamate and overactivation of glutamate receptors [13,14]. Overactivation of glutamate receptors can stress nerve cells to their death in a process called excitotoxicity [12,11]. Because most cells of the nervous system express at least one type of glutamate receptor [11], excitotoxicity can easily damage or kill numerous cells of the nervous system after a seizure. Not only does excitotoxicity

damage/kill cells (contributing to neurodegeneration), but it promotes epitogenesis [66]. Based on this commonality, preventing the accumulation of glutamate may reduce the likelihood of excitotoxicity, thereby suppressing the process of epitogenesis.

In response to excitotoxicity, the brain tries to protect its cells from seizure-induced pathological changes. Unfortunately, these responses are commonalities between epileptic patients that play a role in epitogenesis. For example, neuroinflammation, oxidative stress, and synaptic remodeling are well-known factors of epitogenesis [15,16,12].

An innate response to excitotoxicity is the recruitment of inflammatory factors [66]. While neuroinflammation attempts to rid the brain of harmful material, neuroinflammation causes changes to cell functioning that promote symptoms of neurological disorders and epilepsy [15,16,17,3]. Vilela et al. stated that post-seizure inflammatory mediators, predominantly IL-6 and IL1-β, are important in the development and maintenance of additional epileptic seizures [66,3]. In fact, IL-6 treatment increased seizure severity in murine models of epilepsy [70]. Furthermore, Webster et al. describes that neuroinflammation is a driving factor of seizures in epilepsy and after traumatic brain injuries [66]. These data suggest reducing neuroinflammation after a seizure or traumatic brain injury will reduce the progression of recurrent seizures.

Another innate response to excitotoxicity, is synaptic remodeling [12]. Excitotoxicity not only alters glutamatergic transmission systems, but alters multiple signalling pathways [12]. For example, altered serotonergic transmission systems caused by excitotoxicity is a commonality between epileptic patients [51]. These alterations can be thought of as shifts in connectivity and synchronicity that contribute to epitogenesis. Synaptic remodeling attempts to renormalize neuronal connectivity and synchronicity by strengthening and/or weakening glutamate receptor sensitivity [67,12]. Sadly, these attempts are long-term changes that ultimately contribute to both neuroinflammation and excitotoxicity [67,12]. Based on this commonality between epileptic patients, normalizing Ca^{2+} after a seizure without changing glutamate receptor sensitivity could prevent long-term synaptic changes caused by synaptic remodeling.

Oxidative stress is an effect of excitotoxicity rather than a response. Excitotoxicity causes an imbalance between reactive oxygen/nitrogen species (ROS/RNS) and antioxidant agents [43], also known as oxidative stress. A study by Sudha et al. showed the antioxidant status of the blood of epileptic patients compared to controls. They concluded that oxidative stress is implicated in epitogenesis [44]. Furthermore, studies suggest that oxidative stress not only promotes epitogenesis, but plays a role in the initiation of epilepsy [45]. ROS/RNS are produced by mitochondrial or enzymatic activity [69]. Non-mitochondrial sources of ROS/RNS are activated by seizures, and targeting these enzymes has been shown to attenuate seizure-induced neurodegeneration [68,69]. Studies show that increasing the amount of antioxidants in the blood of epileptic patients reduces epitogenesis and seizure-induced neurodegeneration [68,44].

Altogether, epileptic patients share commonalities that give insight to anticonvulsant targets. These commonalities include: neuroinflammation, altered glutamatergic transmission system, and oxidative stress. Based on these commonalities, anticonvulsant targets would include those that decrease neuroinflammation and oxidative stress while normalizing Ca^{2+}/glutamatergic transmission systems.

B. CBD's Mechanisms of Action

It is well-known that CBD possesses anticonvulsant properties, but CBD's mechanisms of action to accomplish anticonvulsant effects are not fully understood. CBD is a multi-target drug [18], meaning CBD can affect the body by simultaneously interacting with one or more receptors, enzymes, ion channels, etc.. Because CBD is a multitarget drug, there are many proposed mechanisms of action for CBD. The following will describe the possible receptors, enzymes, ion channels, etc. CBD interacts with to decrease neuroinflammation and oxidative stress while normalizing Ca^{2+}/glutamatergic transmission systems.

1. GPR55

CBD's anticonvulsant effects may arise by its interactions with G coupled-protein receptor 55 (GPR55), a receptor that modulates inflammation and the activity of Ca^{2+} channels [48,49,50]. Activation of GPR55 promotes inflammation and increases Ca^{2+}permeability, therefore increases the release of glutamate [47,48,49]. Marichal et al. suggested GPR55's modulation of Ca^{2+} channels plays a role in hippocampal release of glutamate, procedural memory, and motor coordination [46]. Other research confirmed that deletion of GPR55 in mice regulates proinflammatory cytokines [47]. CBD is a potent antagonist at GPR55 [50]. CBD inhibits other GPR55 ligands from promoting Ca^{2+} permeability and proinflammatory responses [50]. Antagonism at GPR55 is a possible mechanism CBD uses to reduce neuroinflammation and normalize Ca^{2+}/glutamatergic transmission systems.

2. 5-HT1A

CBD may interact with serotonin receptors to normalize Ca^{2+}/glutamatergic transmission systems and reduce inflammation. Manford et al. stated that epilepsy causes glutamate-induced abnormalities of the serotonin receptor, 5-HT1A [10]. Abnormally functioning 5-HT1A causes decreased levels of serotonin, a commonality in both epileptic and depressed patients [51]. CBD is a potent agonist at 5-HT1A, which relays anxiolytic effects [52,8] and may partially contribute to CBD's anticonvulsant effects. Some studies suggest 5-HT1A activation mediates anticonvulsant effects such as increasing γ-aminobutyric acid activity and reducing inflammatory cytokines [51,10], however more research is required to verify the anticonvulsant effects of 5-HT1A activation.

Because of the neurological alterations caused by recurrent seizures, epilepsy commonly involves comorbid depression [Kanner2016 Manford2017]. CBD possesses many neuroprotective properties beyond anticonvulsant effects that could improve cognitive and emotional health in epileptic patients. For example, studies show CBD effectively improves cognitive decline associated with neurological disorders [53,54,55], promotes neurogenesis [56,55,57], decreases blood-brain barrier (BBB) permeability [50], and helps maintain a normal heartbeat to supply the brain with oxygen-rich blood [8,58]. These neuroprotective properties of CBD are further discussed in Neuroprotective Properties of Cannabidiol: A Narrative Review [71]. CBD's neuroprotective effects in addition to its anticonvulsant effects could significantly benefit epileptic patients.

3. PPARɣ and A2a

Because neuroinflammation promotes epilepsy progression, anti-inflammatory effects of CBD contribute to its anticonvulsant effects. Though CBD may have alternate mechanisms for inflammatory relief, the majority of researchers attribute the anti-inflammatory properties of CBD to

its interactions with peroxisome proliferator-activated receptor gamma (PPARɣ) [59,7,8,57]. PPARɣ activation inhibits the NF-κB signaling pathway, thereby reducing neuroinflammation [60]. CBD is an agonist at PPARɣ, which relays a progressive vasorelaxant effect [61,62]. This action counterbalances the vasodilation associated with neuroinflammation. Indeed, CBD treatment on murine models of epilepsy showed significant reduction of IL-6 and IL-1β, inflammatory mediators found in excess after epileptic seizures [42,3].

Multiple studies suggest the anti-inflammatory properties are at least partially due to agonism at adenosine receptor 2 (A2a) [63,64]. A2a play a large role in attenuating inflammation. In fact, Ohta et al. showed that genetically-modified mice without A2a are hypersensitive to inflammatory stimuli [65]. Furthermore, the involvement of A2a in CBD's anti-inflammatory properties were confirmed by the use of antagonists [59,50]. PPARɣ and A2a are recognized for their contribution to CBD's anti-inflammatory effects, however activation of these receptors may play a significant role in CBD's anticonvulsant effects.

4. Elevation of Anandamide Levels

Arachidonoyl ethanolamide (anandamide) is an endogenous cannabinoid involved in memory, pain, and convulsive seizures [19,3]. Studies show elevated levels of anandamide is beneficial for epileptic patients [21,4,3,22]. Once synthesized, anandamide activates cannabinoid and non-cannabinoid receptors to relay anticonvulsant effects such as suppressed glutamate release [20,25]. Without the influence of CBD, anandamide is quickly transported to the endoplasmic reticulum where fatty acid amide hydrolase (FAAH) is responsible for inactivating anandamide via catabolism [20]. CBD blocks anandamide transporters, fatty acid binding proteins; therefore, anandamide is not transported to FAAH for degradation and its anticonvulsant effects are prolonged [20,18,3]. Because CBD enables anandamide's anticonvulsant effects, CBD has indirect mechanisms of action to produce anticonvulsant effects.

4a. TRPV1 and TRPA1

A well-recognized target for CBD's anticonvulsant effects are Ca^{2+} channels. As previously stated, increased Ca^{2+} permeability facilitates the release of glutamate, causing overactivation of glutamate receptors, excitotoxicity, and epitogenesis [3,23,11]. CBD normalizes Ca^{2+} permeability through modulation of transient receptor potential (TRP) ion channels. In particular, anticonvulsant effects of CBD are largely attributed to anandamide's interactions with transient receptor potential of vanilloid-type 1 (TRPV1) [23].

CBD indirectly activates TRPV1 through elevated levels of anandamide [4,25], so CBD treatment is expected to produce effects of TRPV1 agonism [18,26]. Without the influence of CBD, TRPV1 activation supports epitogenesis by increasing Ca^{2+} permeability, thereby facilitating the release of glutamate [27,4]. With the influence of CBD, Ca^{2+} permeability normalizes and glutamate release is suppressed [3,4,6,28]. There are two proposed mechanisms of action for this effect: (1) Elevated levels of anandamide activate TRPV1 to a lesser degree than when activated during epitogenesis, meaning activation of TRPV1 by anandamide does not induce sufficient Ca^{2+} permeability for glutamate release [25]. (2) TRPV1 is quickly desensitized by elevated levels of anandamide, leading to inactivation of TRPV1 [3,6,26].

A study testing the effects of CBD on mice with pentylenetetrazole-induced seizures showed TRPV1 playing a large role

in the anticonvulsant effects of CBD [3]. In the study, pretreatment with CBD attenuated electrical activity associated with seizures in mice brains, thereby attenuating seizures. These results were prevented with the use of TRPV1, CB1, and CB2 antagonists, meaning TRPV1, CB1, and/or CB2 play a key role in CBD's anticonvulsant effects.

Transient receptor potential ankyrin-type 1 (TRPA1) is a type of TRP channel often coexpressed with TRPV1. Like TRPV1, activated TRPA1 increases Ca^{2+} permeability and promotes the release fo glutamate [4,29]. CBD indirectly activates TRPA1 through anandamide, which has very high efficacy at TRPA1 compared to other cannabinoids and environmental stimuli [24]. De Petrocellis et al. described CBD as a potent desensitizer of TRPA1 [30]. CBD's ability to normalize Ca^{2+} could arise from desensitization of TRPA1, therefore TRPA1 may play a role in the anticonvulsant effects of CBD.

4b. CB1 and CB2

CBD has low binding affinity for cannabinoid receptors 1 (CB1) and 2 (CB2), however some research suggests anandamide may interact with these receptors to produce anticonvulsant effects [31]. Some believe that elevated levels of anandamide activate CB1 to reduce glutamatergic transmission [31,21]. Activation of CB1 blocks voltage gated calcium channels and reduces neurotransmitter release [32,23]. This mechanism of action is not well-recognized in CBD research and is contradicted by recent studies. Recent studies suggest that CBD is a negative allosteric modulator or antagonist at CB1, meaning CBD inhibits the activation of CB1 [33,34]. Though CBD's ability to elevate anandamide levels is well-known, it is unlikely that anandamide interacts with CB1 to contribute to CBD's anticonvulsant effects. Instead, CBD is thought to suppress psychoactive effects by inhibiting activation of CB1 [33,34].

Some anti-inflammatory properties of CBD may arise from indirect activation of CB2 [35]. CB2 is expressed on the inflammatory mediators recruited in response to excitotoxicity [67]. Because neuroinflammation promotes the progression of epilepsy, CB2 could contribute to CBD's anticonvulsant effects. Activation of CB2 by anandamide negatively regulates inflammatory responses [25]. In fact, human and murine models show anandamide downregulating inflammation by reducing cytokine release and nitric oxide production [36,37,38]. This mechanism of action is not largely recognized in research associated with CBD's anticonvulsant properties.

5. Reactive Oxygen/Nitrogen Species

As previously stated, oxidative stress promotes epitogenesis and seizure-induced neurodegeneration. CBD is a strong antioxidant due to two hydroxyl groups in its chemical composition that donate electrons to scavenge reactive oxygen/nitrogen species and prevent lipid peroxidation [39]. CBD shows potent antioxidant action against reactive oxygen species, nitrite production, and nitric oxide synthase expression [40,41,42], suggesting its antioxidant properties contribute to its anticonvulsant effects. In addition, the antioxidant action of CBD may be enhanced by elevation of anandamide. Anandamide acts as an antioxidant during oxidative stress conditions [20]. Because CBD inhibits the degradation of anandamide, the antioxidant action of anandamide may assist CBD in reducing oxidative stress [20].

Conclusions

Some epileptic patients are resistant to antiepileptic drugs, therefore the need arises for alternative anticonvulsant agents.

Preclinical and clinical studies repeatedly show effective anticonvulsant effects of CBD. CBD treatment reduces epitogenesis by normalizing intracellular Ca^{2+}/glutamatergic transmission, reducing neuroinflammation, and reducing oxidative stress. Though CBD is widely recognized for its anticonvulsant effects, its exact mechanisms of action are unknown. CBD enhances levels of anandamide, an endocannabinoid with anticonvulsant properties, which expands its possible anticonvulsant targets. Based on literature to date, CBD can modulate intracellular Ca^{2+} through TRPV1, TRPA1, and/or GPR55. The antioxidant properties of CBD and anandamide act to reduce reactive oxygen/nitrogen species, thereby reducing oxidative stress. CBD may reduce neuroinflammation by activating PPARɣ, A2a, and/or CB2. Because CBD produces anxiolytic effects through 5-HT1A, CBD may also be beneficial for epileptic patients with comorbid depression. While this narrative review discusses trials to 4 November 2019, exponential research on the therapeutic effects of CBD is expected. The current data on the CBD's anticonvulsant effects suggests CBD is an effective treatment option for epileptic patients of all ages.

Declarations

Availability of Data and Materials: The datasets analyzed during the current study are available in the University of Montevallo Carmichael Library or PubMed repositories, https://www.ncbi.nlm.nih.gov/pubmed/ , http://libguides.montevallo.edu/index?group_id=15001

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