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Cannabinoids, hippocampal excitability and efficacy for the treatment of epilepsy

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ABSTRACT

Interest in cannabis and its related cannabinoids THC and CBD for use as anti-convulsant therapy has been progressively increasing. While the destigmatization of cannabis and cannabis related research have progressed in the last few decades, there are still many questions that remain unanswered. This review seeks to summarize the progress made in cannabis research in the past four decades and to identify possible directions for future research that are critical for the development of cannabinoid-based therapy in epilepsy.

Contents

1. Introduction

While the use of the cannabis plant (*Cannabis sativa*) goes back thousands of years, research on the active substances and uses of cannabis began much more recently (Pertwee, 2006). The recent approval of the anti-epileptic medication Epidiolex® (James & Kight, 2018) is a manifestation of the continual interest in the use of cannabis-based products in the treatment of seizure disorders. The importance of the hippocampus in epilepsy and seizure disorders is well known (Chatzikonstantinou, 2014) and the presence of an abundance of cannabinoid receptors in the hippocampus (Herkenham et al., 1990) makes it a particularly exciting subject for research seeking novel targets for anti-epileptic therapies.

2. History

Cannabis plant extracts contain >120 active compounds known as phytocannabinoids (Morales, Hurst, & Reggio, 2017). The

Abbreviations: THC, (−)-*trans*-^{9}-tetrahydrocannabinol; 2-AG, 2-arachidonoylglycerol; CBD, Cannabidiol; CB1, Cannabinoid receptor 1; CB2, Cannabinoid receptor 2; CBDV, Cannabidivarin; DSE, Depolarization-induced suppression of excitation; DSI, Depolarization-induced suppression of inhibition; LTD, Long-term depression; MSE, Metabotropic-induced suppression of excitation; MSI, Metabotropic-induced suppression of inhibition; anandamide, N-arachidonylethanolamide.

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phytocannabinoids found in *cannabis* extractions vary in abundance, the most abundant of which is (−)-*trans*-^{9}-tetrahydrocannabinol also known as ^{9}THC or THC. Another phytocannabinoid that received a lot of attention and publicity in the recent years is cannabidiol (CBD). Phytocannabinoids such as THC or CBD that have been isolated from the other compounds within a cannabis extraction are known as exogenous cannabinoids (Morales et al., 2017).

In 1988 the first receptor that bound to THC was discovered in rats (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988) and cloned (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990). Soon after, a human counterpart, later named cannabinoid receptor 1 (CB1), was also discovered and cloned (Gérard, Mollereau, Vassart, & Parmentier, 1991). A couple years later another cannabinoid receptor, named cannabinoid receptor 2 (CB2) was discovered and cloned (Munro, Thomas, & Abu-Shaar, 1993). These two receptors have a high homology in their amino acids sequence and are thus known as subreceptors (Howlett & Abood, 2017). As such, the different characteristics and effects of the many types of cannabinoid compounds are determined by their affinity to each of the different sub receptors, which collectively are known as the affinity profile for that substance. The discovery of endogenous receptors that respond to exogenous cannabinoids suggested the existence of an endogenous ligand that would also bind to this receptor. And indeed, Narachidonylethanolamide (anandamide), an arachidonic acid metabolite, was shown to activate CB1 (Devane et al., 1992). Later on, a second metabolite, 2-arachidonoylglycerol (2-AG), was identified to bind to cannabinoid receptors as well (Mechoulam et al., 1995; Sugiura et al., 1995).

The discovery of endogenous cannabinoids and endogenous cannabinoid receptors lead to ideation of the "endocannabinoid system" which describes the endogenous cannabinoids and cannabinoid receptors in the body. Furthermore, cannabinoids have also been found to act on several other receptors outside of what is traditionally thought of as the endocannabinoid system (Howlett & Abood, 2017).

CB1 and CB2 receptors are found in numerous places throughout the body (Howlett & Abood, 2017). CB1 receptors are found mostly on neurons in both the central and peripheral nervous systems but are particularly abundant in the cortex, basal ganglia, hippocampus, and cerebellum (Herkenham et al., 1990). CB2 receptors are found on immune cells in peripheral organs such as the spleen but not in healthy brain tissue (Glass, Dragunow, & Faull, 1997; Howlett et al., 2002; Munro et al., 1993). CB1 (Matsuda et al., 1990) and CB2 (Munro et al., 1993) are both G-protein coupled receptors and work primarily through the Gi/o pathway which inhibits adenylate cyclase activity (Howlett, Qualy, & Khachatrian, 1986). Due to the wide distribution of CB1 and CB2 in the body, the effects of CB1 and CB2 are many and include antiepileptic, analgesic, antiemetic, neuroprotective, anti-inflammatory actions as well as the notable psychotropic effects (Grotenhermen & Müller-Vahl, 2012). The many effects of cannabinoid compounds have been the subject of much research for therapeutic use including reduction in chronic pain, chemotherapy induced nausea, weight loss and anorexia in patients with AIDS, sleep disorders, and Tourette's Syndrome (Whiting et al., 2015). In addition, recent clinical trials have shown cannabinoids to also be of use in certain forms of epilepsy (James & Kight, 2018). Since the discovery of the CB1 and CB2 receptors many compounds have been found that interact with these receptors. The ligands of the CB1 and CB2 receptors have been separated into five classes based upon characteristic features of their molecular structure. The first group of cannabinoid receptor ligands are the classic cannabinoids which are derived from dibenzopyran and include 9-THC (a partial CB1 agonist) and 8-THC-dimethylheptyl, a synthetic analog of (−)- 8-tetrahydrocannabinol that has higher CB1 and CB2 activity than 9- THC. The second group is known as nonclassical cannabinoids which is composed of bicyclic and tricyclic ^{9}-THC analogs that lack a pyran ring. This group includes (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]*trans*-4-(3-hydroxypropyl)cyclohexanol (CP55940) which has both CB1 and CB 2 activity. The third group of cannabinoids are the indole derived cannabinoids which include *R*- (+)-[2,3dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1naphthalenylmethanone mesylate [*R*-(+)-WIN55212] a CB1 and CB2 ligand that has stronger CB2 affinity compared to CB1. The fourth group of cannabinoids are the eicosanoid cannabinoids which includes the endogenous cannabinoids such as anandamide as well as 2-AG. Finally, the fifth group is composed of cannabinoid receptor antagonists, which may show a strong specificity toward either CB1 or CB2 (Pertwee et al., 2010) (Fig. 1).

Currently, the United States Food and Drug Administration has approved four cannabis-based medicines for consumer use. Dronabinol (Marinol®), a synthetic ^{9}THC, as well as Syndros®, a liquid preparation of Dronabinol, have been approved for use in chemotherapy associated nausea and vomiting as well as appetite stimulation in AIDS patients effected by wasting. Nabilone, a synthetic analog of ^{9}THC has also been approved for use as an alternative to Dronabinol in similar situations (National Academies of Sciences, 2017). In addition, Epidiolex®, a CBD oil extracted from the cannabis plant has also been approved for use in Dravet syndrome and Lennox-Gastaut syndrome, two anti-epileptic resistant forms of childhood epilepsy (James & Kight, 2018). Outside of the United States, Nabiximol (Sativex®), a combined ^{9}THC and CBD oromucosal spray has been approved for use in 27 countries for pain relief in multiple sclerosis and cancer patients. In addition to the synthetic cannabinoids and cannabis extracts of THC and CBD, many patients also use cannabis plant directly to treat symptoms most often through smoking or ingesting the plant which would contain not only the active THC and CBD compounds, but also all of the other phytocannabinoids present in the cannabis plant such as tetrahydrocannabivarin or cannabinol (National Academies of Sciences, 2017). Both pharmaceutical and non-pharmaceutical preparations of cannabis can have some degree of variation in dosage and formulation and regulation and quality control of cannabis and cannabis derived products is a point of ongoing development (Thomas & Pollard, 2016).

3. Metabolism and bioavailability of CBD and THC

The absorption of THC is highly dependent on its route of administration. Smoking or inhaling vaporized THC showed the fastest absorption with peak plasma levels being reached after 10 min. Oral administration of THC showed a slower absorption with peak plasma levels being reached after 2–6 h. The bioavailability of THC is also dependent on the route of administration where smoking THC has a bioavailability of about 25%, vaporized THC has a bioavailability of 10–35%, and oral administration of THC has a bioavailability of about 6% (Gaston & Friedman, 2009). Once absorbed in the body, THC travels in the blood bound to proteins and is highly lipophilic with a volume of distribution of 3.4 L/Kg. Metabolism occurs in the liver where THC is hydroxylated into 11-OH-THC by Cytochrome P450 enzymes, CYP2C9, 2C19, and 3A4. 11OHTHC is then further broken down into over 30 different metabolites which are excreted in the feces (65%) and urine (25%) (Huestis, 2007). The half-life of THC has been measured to be approximately 25–36 h (Grotenhermen, 2003). Like THC, the absorption of CBD and cannabidivarin (CBDV) heavily depends on the route of administration. Oral administration of CBD reaches peak plasma concentrations after 2 h in animal studies (Deiana et al., 2012) whereas intranasal CBD was absorbed in 10 min, and transdermal gels were absorbed in 15.5 h (Ohlsson et al., 1986). CBD and CBDV have a low oral bioavailability <10% (Devinsky et al., 2014). One significant reason for the low oral bioavailability is the high first-pass metabolism that occurs in the gut and liver which results in poor absorption from the GI tract (Stout & Cimino, 2014). Like THC, Cannabidiol is highly lipophilic and travels in the blood bound to proteins. Cannabidiol also has a volume of distribution of 32 L/kg (Ohlsson et al., 1986). In the liver CBD and CBDV are hydroxylated into 7-OH-Cannabidiol by Cytochrome P450 enzymes,

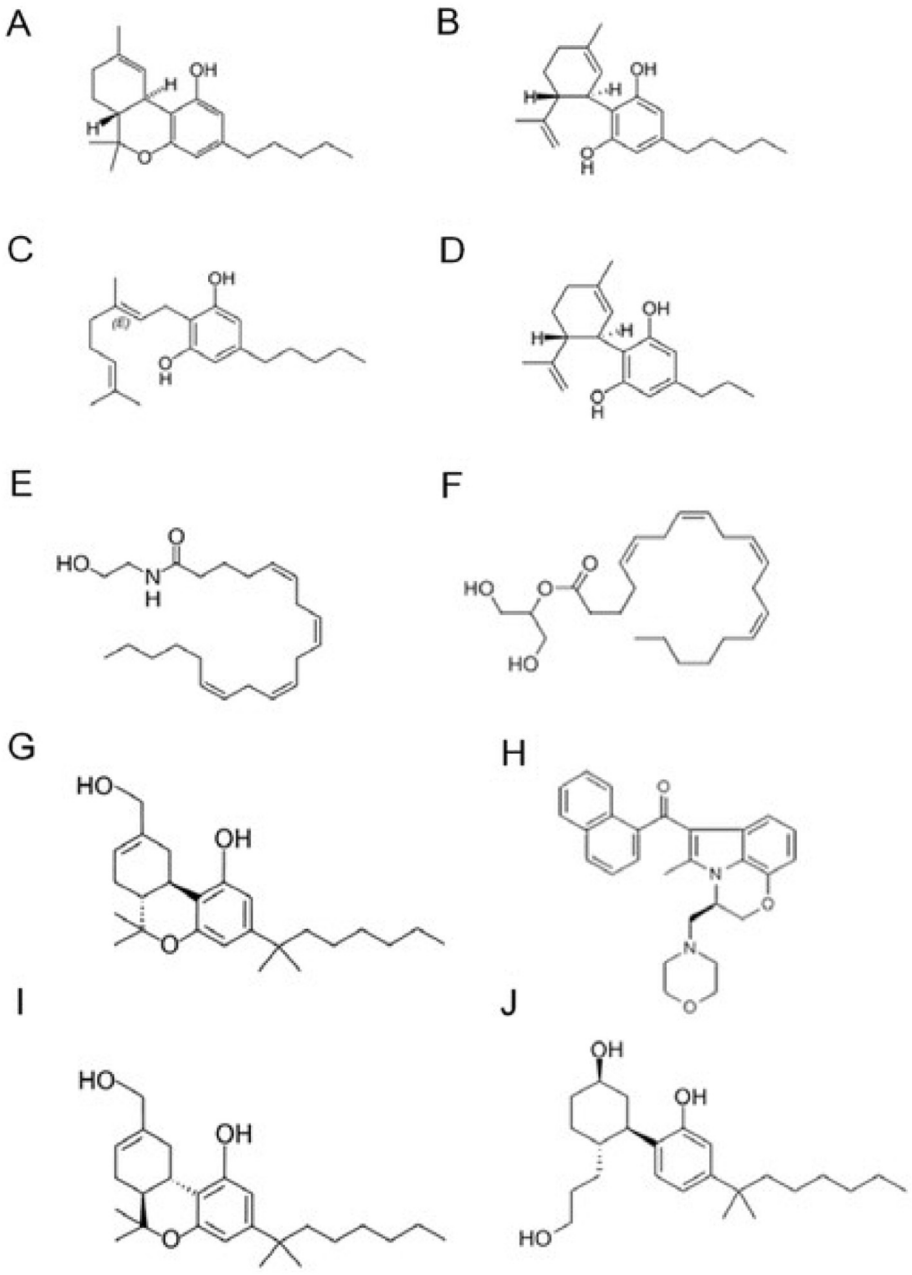

Fig 1. (A) Delta9-tetrahydrocannabinol (delta9-THC); (B) cannabidiol (CBD); (C) cannabigerol (CBG); (D) cannabidivarin (CBDV); (E) anandamide (AEA); (F) 2-arachidonyl glycerol (2-AG); (G) HU210; (H) WIN55, 212–2; (I) HU211; (J) CP55940; (A)–(D) natural cannabinoids; (E) and (F) endocannabinoids; (G)–(J) synthetic cannabinoids. Hayakawa et al., 2010.

CYP2C19 and CYP3A4 primarily, but CYP1A1, 1A2, 2C9, and 2D6 may also be involved (Zendulka et al., 2016). The Cannabidiol metabolites are then excreted, mostly in the feces but a small portion is also excreted in the urine (Gaston & Friedman, 2009).

4. Physiology of cannabinoids in the hippocampus

As discussed previously, CB1 receptors, one of the most abundant G-protein coupled receptors in the CNS, are found in particularly high concentrations in the hippocampus (Herkenham et al., 1990), while CB2 receptors, characteristic of peripheral cells, are generally not found in the CNS (Munro et al., 1993). Radiographic studies have shown a high level of cannabinoid receptors throughout the hippocampus including CA1–3 with the highest levels in the dentate gyrus (Glass et al., 1997). CB1 receptors in the hippocampus have been further characterized to be primarily located on presynaptic GABAergic neurons of CCK containing basket cells (Irving et al., 2000; Katona et al., 1999; Tsou, Mackie, Sañudo-Peña, & Walker, 1999). More recent research also supports the existence of CB1 receptors on excitatory hippocampal neurons as well (Kawamura et al., 2006). In addition to the traditional CB1 and CB2 receptors, studies done using CB1 knockout mice show the possible existence of novel endocannabinoid receptors within the hippocampus that also play a role in hippocampal signaling, however further study and characterization of these receptors is still required (Breivogel, Griffin, Di Marzo, & Martin, 2001; Hájos, Ledent, & Freund, 2001).

Research on the physiological effects of CB1 activity in the hippocampus has focused on its effects of modulating neurotransmitter release in presynaptic neurons. Many studies have shown that CB1 activity has an inhibitory effect on neurotransmitter release in excitatory glutaminergic neurons (Shen, Piser, Seybold, & Thayer, 1996), cholinergic neurons (Gessa, Casu, Carta, & Mascia, 1998; Gifford, Bruneus, Gatley, & Volkow, 2000; Giovana, Felice, & Luigi, 1998), and inhibitory GABAergic neurons (Katona et al., 1999; Katona et al., 2000). The activation of CB1 receptors in presynaptic neurons was shown to

inhibit voltage-gated Ca2+ channel activity and increase K+ channel activity similar to other G-protein coupled receptors that inhibit presynaptic transmission (Shen et al., 1996). Outside of the direct inhibition of CB1 activity on presynaptic neurotransmitter release, endocannabinoids, namely anandamide and AG-2, have been shown to play a major role in presynaptic neurotransmitter release and synaptic plasticity. One of the most well studied phenomena regarding endocannabinoid activity is known as depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE). DSI and DSE refer to postsynaptic feedback inhibition of presynaptic inhibitory (GABA) and excitatory (glutamate) neurotransmitter release. In DSI and DSE, frequent depolarization of the postsynaptic neuron causes an increase in Ca2+ levels in the dendrite which stimulates endocannabinoid synthesis (Pitler & Alger, 1992; Stella & Piomelli, 2001). These endocannabinoids travel in a retrograde fashion to bind to presynaptic CB1 receptors that decrease presynaptic neurotransmitter release through the G_i pathway resulting in blockage of Ca2+ channels and stimulation of K+ channels which inhibit neurotransmitter release (Kreitzer & Regehr, 2002; Wilson, Kunos, & Nicoll, 2001). A mechanism for increased endocannabinoid synthesis independent of postsynaptic Ca2+ elevation has also been described and is known as metabotropic-induced suppression of inhibition (MSI) and excitation (MSE) (Ohno-Shosaku, Hashimotodani, Maejima, & Kano, 2005). In MSI and MSE activation of Group I metabotropic glutamate receptors as well, M1, or M3 muscarinic receptors cause an increase in endocannabinoid synthesis via phospholipase Cß and diacylglycerol lipase (Ohno-Shosaku et al., 2005; Sugiura, Kobayashi, Oka, & Waku, 2002). The synthesized endocannabinoids are thought to act in a manner similar to DSI and DSE by traveling in a retrograde direction to the presynaptic neurons where they bind to CB1 receptors thereby inhibiting neurotransmitter release (Chevaleyre, Takahashi, & Castillo, 2006). In addition to the short-term modification of presynaptic neurotransmission described above, another form of endocannabinoid mediated change in synaptic plasticity observed in the hippocampus is a heterosynaptic form of long-term depression (LTD). In heterosynaptic LTD, continual activation of glutaminergic signaling via the Schaffer Collaterals and subsequent activation of metabotropic glutamate receptors results in increased endocannabinoid synthesis and long-term presynaptic inhibition of adjacent presynaptic GABAergic inhibitory neurons (Chevaleyre & Castillo, 2003).

5. Preclinical studies on cannabinoid action in the hippocampus

Clinical interest in cannabinoids for seizure control has included THC but has focused primarily on CBD. Both CBD and THC have previously been shown to have anti-convulsant effects with THC working primarily through a CB1 dependent mechanism and CBD working through a more complex mechanism (Wallace, Wiley, Martin, & DeLorenzo, 2001). In addition to the direct agonist effect of THC on CB1, THC also mediates the endocannabinoid system discussed above which was found to have a significant effect in controlling the seizure threshold in temporal lobe epilepsy (Wallace et al., 2003).

Interestingly, THC also had an antagonistic effect on DSI/DSE, MSI/MSE, and heterosynaptic LTD (Straiker & Mackie, 2005; Straiker & Mackie, 2007). The mechanism of CBD mediated anti-convulsant effects is more complex than that of THC. CBD is an antagonist of CB1where it works as a negative allosteric modulator (Tham et al., 2018). Although this may appear to conflict with the anti-epileptic activity shown through THC activation of CB1, one study with mice pretreated with a CB1 selective inhibitor (SR141716A) demonstrated a loss of THC mediated anti-epileptic effects, but not of CBD effects (Wallace et al., 2001). The persistence of the anti-epileptic effects of CBD indicate that the mechanism for anti-epileptic effects occurs through other pathways that are independent of CB1. This is supported by CBD's activity at a multitude of other receptors within the CNS and the hippocampus making it known as a "multitarget" compound (Devinsky et al., 2014). CBD acts as an agonist to the $5HT1_A$ receptor, the transient receptor potential of ankyrin type 1 channel, and the transient receptor potential of vanilloid type 1 and 2 channels. CBD also functions as an antagonist at the G-protein-coupled receptor GPR55, the transient receptor potential of melastatin type 8 channel, and fatty acid amide hydrolase which degrades amantadine (Devinsky et al., 2014; Jones et al., 2010). The many targets of CBD lend many possible pathways through which it may exert its anti-convulsant activities, although currently the exact mechanism is not yet known (Devinsky et al., 2014). Many preclinical studies have been done concerning the anti-convulsant effects of cannabinoids and the endocannabinoid system. Endocannabinoids in particular have been shown to play a neuroprotective role in the setting of acute seizure activity. Studies using Kainic acid induced seizures revealed an increase in anandamide 20 min after the seizure and pilocarpine induced seizures showed an increase in 2-AG levels 15 min after the seizure (Marsicano et al., 2003;

Wallace, Blair, Falenski, Martin, & DeLorenzo, 2003). This finding suggests that endocannabinoids are synthesized and released "on-demand" in response to seizure activity (Marsicano et al., 2003). Furthermore, pretreatment with anandamide reuptake inhibitor UCM707 and fatty acid amide hydrolase inhibitor AM374 increased endocannabinoids in the neurons and resulted in a protective effect against kainic acid induced seizures (Karanian et al., 2007; Naidoo et al., 2012).

The activation of CB1 receptors was also found to reduce the severity of seizures in animal models with kainic acid induced seizures. In addition, the deletion of CB1 receptors resulted in an increase in postictal cellular apoptosis whereas overexpression of CB1 receptors resulted in a decrease in seizure severity and cell death (Guggenhuber, Monory, Lutz, & Klugmann, 2010; Monory et al., 2006). In addition to its' anticonvulsant and neuroprotective effects in acute seizure models, CB1 is also an important component of the homeostatic response of the nervous system in modulating seizure activity in the hippocampus. Seizure activity in the hippocampus resulted in an increased expression of CB1 receptors in dentate gyrus and CA1–3 (Alger, 2014; Falenski, Blair, Sim-Selley, Martin, & DeLorenzo, 2007). This compensatory response discriminates between excitatory and inhibitory interneurons, with excitatory glutaminergic interneurons showing increased CB1 expression and inhibitory GABAergic neurons showing decreased CB1 expression, with both of these changes functioning to reduce hippocampal excitability (Alger, 2014; Katherine W Falenski et al., 2009; Ludányi et al., 2008; Bhaskaran & Smith, 2010; Wyeth, Zhang, Mody, & Houser, 2010). Furthermore, tissue samples from epileptic subjects showed decreased expression of CB1 on glutaminergic neurons and increased expression in GABAergic neurons suggesting that impaired CB1 homeostasis may be involved in development of chronic seizure disorders (Karlócai et al., 2011; Ludányi et al., 2008).

A relatively recent review of cannabinoid usage in epilepsy generated a good profile of the current research of the anti-convulsant effects of synthetic cannabinoids and phytocannabinoids in animal models (Rosenberg Evan, Tsien Richard, Whalley Benjamin, & Orrin, 2015). The review found 34 studies on THC in animal models, of which, 21/34 (61.8%) demonstrated anticonvulsant effects, 1/34 demonstrated proconvulsant effects (2.9%), and 11/34 showed no significant effect (32.4%). 41 studies were found using CBD in animal models, of which 33/41 (80.5%) showed that CBD had an anticonvulsive effect and 8/41 (19.5%) showed that CBD was ineffective for reducing seizures in mice and rats (Rosenberg Evan et al., 2015). In addition to these findings, more recent studies continue to be made regarding the anti-convulsant effect of CBD in animal models. One such example includes our previous experiment on the protective effect CBD has on LTP in pilocarpine induced status epilepticus (Maggio, Stein, & Segal, 2018). Together this data suggests that THC and CBD both have some anti-convulsant effect in animal models.

In addition, the study also reviewed the effects of synthetic modulators of CB1 and endocannabinoid activity, revealing more mixed results. The review of CB1 agonists identified 47/69 (68.1%) studies that showed

an anticonvulsant effect, 2/69 (2.9%) that showed a proconvulsant effect, and 15/69 (21.7%) that showed no significant effect in animal models. However, CB1 antagonists were only pro-convulsant in 7/18 (38.9%) of studies, anti-convulsant in 1/18 (5.6%) of studies, and had no anti-convulsant effect in 10/18 studies. This combined with the results for endocannabinoid upregulating drugs (inhibitors of fatty acid amide hydrolase and anandamide reuptake) which showed 6/13 (46.2%) anticonvulsant activity, 3/13 (23.1%) mixed effect, and 4/13 (30.8%) no significant anti-convulsant effect suggest that although CB1 activation of the endocannabinoid system did show neuroprotective effects as discussed above, it may not have the same efficacy in reducing seizure severity (Rosenberg Evan et al., 2015).

6. Clinical studies on cannabinoid effectiveness in epilepsy

The study of cannabinoids in epilepsy has also been extended to human subjects. These studies are primarily composed of case reports, epidemiological studies, and surveys and are primarily focused on the anti-convulsant effects of CBD. Case reports are usually used oral cannabis extracts with high CBD:THC ratios. One report consisting of 74 children with intractable epilepsy from five Israeli pediatric centers reported a reduction in seizure frequency in 66/74 (89%) of these patients, while 28/74 (38%) reported a >50% reduction in seizure frequency (Tzadok et al., 2016). Another case study done in Colorado included 75 pediatric patients of which 25/75 (33%) reported a >50% reduction in seizure frequency (Press, Knupp, & Chapman, 2015). Other case reports include a 5-year-old girl with Dravet Syndrome that experienced a > 90% reduction in seizure frequency (Maa & Figi, 2014) as well as a 40-year old man with focal epilepsy who became seizure free after cannabis use but experienced a recurrence of seizure when cannabis was discontinued (Growers, 1881). Common side effects reported among these studies were somnolence and fatigue (O'Connell, Gloss, & Devinsky, 2017). Few surveys have been done specifically on CBD use in epilepsy include one survey among a Facebook group for parents of children with treatment resistant epilepsy that included 19 children. Of these children, 16/19 (84%) reported improvement with CBD and THC containing extracts and 2/19 (11%) became seizure-free (Porter & Jacobson, 2013). Another survey was done including 117 children 53 of which had infantile spams or Lennox-Gastaut Syndrome. The results of the survey had 85% of the participants report a reduction in seizure frequency and 14% report that they were seizure free (Hussain et al., 2015).

A few clinical studies have also been conducted using isolated CBD. Three placebo-controlled studies were identified with two studies reporting significant anti-seizure effects compared to placebo (Cunha et al., 1980; Mechoulam & Carlini, 1978). One study of 12 patients showed no difference between the 6 in the treatment group and the 6 in the placebo groups (Trembly & Sherman, 1990). The largest study has been performed recently with 214 children with severe childhood epilepsy, 33 of which had Dravet Syndrome and 21 had Lennox-Gastaut syndrome, found that CBD may have some effect in reducing seizure frequency and that it may also have an acceptable safety profile for use in children and adults (Devinsky et al., 2016). A review of the side effects of CBD use also found that the use of CBD in epilepsy treatment yielded side effects that were “generally mild and infrequent” (Iffland & Grotenhermen, 2017). Due to these studies as well as successful FDA trials, Epidiolex®, a CBD cannabis extract has now been approved for use in the U.S. for Dravet Syndrome and Lennox-Gastaut syndrome (James & Kight, 2018). Very few studies have been done using isolated THC and results using THC have been more limited. One such study showed the successful use of THC in pediatric patients with treatment resistant epilepsy, this study had a small population and more research in this area is required (Lorenz, 2004).

Studies have also been done using patients who are treated or self-treat with cannabis plant either through smoking or direct consumption, however, the results have been mixed. Although some studies show an improvement in both seizure severity and seizure frequency in epileptic patients that use cannabis (Gross, Hamm, Ashworth, & Quigley, 2004), others report either no improvement (Hamerle, Ghaeni, Kowski, Weissinger, & Holtkamp, 2014) or even worsening of seizures after cannabis administration.

7. Drug-drug interactions

THC and CBD are not only metabolized by the Cytochrome P450 system in the liver, they also have a significant effect on certain P450 enzymes making drug-drug interactions a significant concern in their utilization. A review of cannabinoid interactions with CYP enzymes found that CBD did have a clinically significant inhibition of CYAP1A1, 2B6, 2C19, and 3A5 as well as an induction effect on CYP 2B. THC interaction with CYP enzymes, however, was deemed to be too weak to cause clinically significant reactions. This is due to the high dose required to elicit the CYP inhibition compared to a normal does of a CBD/THC cigarette (Zendulka et al., 2016). Data on the drug-drug interactions between cannabinoids and anti-epileptics are still lacking however a couple of studies have demonstrated a significant interaction between CBD and clobazam and Ndesmethylclobazam (the active metabolite of clobazam), as well as topiramate, zonisamide, eslicarbazepam, and rufinamide all of which were significantly increased in patients who took CBD (Gaston et al., 2017). One study in mice also showed an increased efficacy of phenytoin but decreased the efficacy of chlordiazepoxide, clonazepam, trimethadione and ethosuximide (Consroe & Wolkin, 1977). In addition to the effect of CBD on other anti-epileptic drugs, CBD and THC are both primarily metabolized by CYP2C19 and CYP3A4, thus making them susceptible to drug-drug interactions with inducers and inhibitors of these enzymes (Gedde, 2016; Grotenhermen, 2003; Stout & Cimino, 2014).

8. Safety profile of CBD in epilepsy

A variety of studies have been done regarding the safety profile of CBD in epilepsy treatment. A review of cannabis use in pediatric epilepsy encompassing four randomized clinical trials and seventeen non-randomized studies was generally inconclusive regarding many of the side effects of CBD in epilepsy treatment. The studies included showed either no effect, improved, and.

impaired sleep, some incidence of GI symptoms, as well as some more serious adverse effects with a low degree of certainty, including status epilepticus and death (Elliott et al., 2019) While it is unclear if these side effects were caused by the CBD treatment, the underlying condition, or other factors, additional data is still needed to further clarify the role CBD plays in these adverse effects.

The side effect of CBD on the comorbidities of epilepsy appear to be minimal as one review CBD was found to have some anti-psychotic and anxiolytic effect with no significant side effects (Iffland & Grotenhermen, 2017). However, as mentioned above, CBD does play role in drug metabolism and the careful monitoring of patients for drug-drug interactions may be important to prevent adverse effects (Tables 1 and 2).

Table 1
Possible effects of CBD on anti-epileptic drugs.[a,b,c]

Drug levels may rise	Drug levels may fall
Topiramate	Carbamazepine
Rufinamide	Chloridiazepoxide
Eslicarbazepam	Trimethadione
Phenytoin	Ethosuximide
Zonisamide	Clonazepam
Clobazam	

[a] Geffrey, Pollack, Bruno and Thiele (2015).
[b] Gaston et al. (2017).
[c] Consroe and Wolkin (1977).

Table 2
Possible effects of anti-epileptics on CBD and THC levels.[a]

May increase CBD and THC Levels	May decrased CBD and THC
Diazepam	Carbamazepine
	Phenobarbital
Midazolam	Phenytoin
	Primidone
Stiripentol	Stiripentol
	Felbamate
Valproic acid	Oxcarbazepine
	Rufinamide
	Topiramate

[a] Iffland and Grotenhermen (2017).

9. Conclusion

The last 30 years of research into cannabis have revealed much about the workings of cannabinoids and the endocannabinoid system within the body. CBD remains an exciting subject of research for anti-convulsant treatment due to its anti-convulsant effects in preclinical trials. However, although more human studies have been performed recently, there is still much work to be done in terms of clinical research and human trials before additional applications of cannabinoids may be developed into treatments for epilepsy. Specifically, despite promising initial results, it is not completely clear what the value of CBD treatment in epilepsy could be. Research in pediatric patients has found that CBD can reduce seizure frequency in epilepsies with specific genetic background, however, whether this effect could be obtained in epileptic disorders of different etiology is currently not known. Furthermore, the potential of CBD as a single therapy in epilepsy has not yet been explored. In the current trials, CBD has always been administered together with conventional antiepileptic drugs. Due to the fact that CBD may either potentiate or decrease the concentrations of antiepileptic drugs, there is a possibility that the effects of CBD may be due to the pharmacokinetic properties.

of this drug and not to a specific antiepileptic mechanism. In this respect, the potential of CBD to cause harm has also not been appropriately addressed and many questions remain unanswered. For example, if CBD affects the concentrations of conventional antiepileptic drugs, what is the level of toxicity that patients are exposed to? Additional research should also address the effects of CBD on epileptic comorbidities. While THC is known to have clear psychotropic effects, the effects of CBD on cognitive and emotional disturbances have not been thoroughly investigated. Therefore, whether CBD would either enhance or diminish personality disorders, anxiety, depression, learning disabilities associated to some epileptic disorders remains a possibility. Finally, the role of CBD in Sudden Unexpected Death in Epilepsy (SUDEP) must still be explored and it is unknown whether CBD may reduce or increase these adverse events.

The many questions related to the use of CBD in epilepsy that have been left unanswered reflects the need of more research on the role of cannabinoids in the treatment of epilepsy. Additional research is also needed in order to understand the potential role of additional cannabinoids derivates (other than CBD and THC) in the treatment of epilepsy.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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