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Cannabidiol in canine epilepsy

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ABSTRACT

The anticonvulsant effect of cannabidiol (CBD), which has been confirmed by findings from animal models and human trials, has attracted the interest of veterinary practitioners and dog owners. Moreover, social media and public pressure has sparked a renewed awareness of cannabinoids, which have been used for epilepsy since ancient times. Unfortunately, at this moment veterinarians and veterinary neurologists have difficulty prescribing cannabinoids because of the paucity of sound scientific studies. Pharmacokinetic studies in dogs have demonstrated a low oral bioavailability of CBD and a high first-pass effect through the liver. Administering CBD in oil-based formulations and/or with food has been shown to enhance the bioavailability in dogs, rats and humans. Tolerability studies in healthy dogs and dogs with epilepsy have demonstrated that CBD was safe and well tolerated with only mild to moderate adverse effects. In this context, it should be noted that the quality of available CBD varies widely, underscoring the importance of pharmaceutical quality and its control. One clinical trial in dogs with drug-resistant idiopathic epilepsy failed to confirm a difference in response rates between the CBD group and the placebo group, while in another cross-over trial a $\geq$ 50 % reduction in epileptic seizure frequency was found in six of 14 dogs in the treatment phase, a reduction that was not observed during the placebo phase. Based on the current state of knowledge it is not possible to provide clear-cut recommendations for the use of CBD in canine epilepsy. Randomized controlled canine trials with large sample sizes are needed to determine the range of therapeutic plasma concentrations, develop evidence-based dosing regimens, determine the efficacy of cannabidiol in drug-refractory epilepsy, and explore potential associations between treatment effects and different etiologies, epilepsy types, and drug combinations.

Introduction

While early reports about a possible medical benefit from cannabis-based preparations date back to about 2700 BCE (Friedman and Sirven, 2017), it is only in the last decade that evidence has been obtained from open-label and placebo-controlled randomized trials demonstrating the antiseizure efficacy of CBD in human patients suffering from genetic syndromes with refractory seizures (Devinsky et al., 2017; Devinsky et al., 2018; Patel et al., 2021; Thiele et al., 2021).

Available information from human medicine has sparked the interest of veterinarians and dog owners. This interest has been confirmed in an US online survey, which evaluated the veterinarians' perception, view and knowledge concerning the use of CBD for therapy in canine patients (Kogan et al., 2018). Seizures were among the top three conditions for which either clients requested information or veterinarians initiated a conversation about a possible use of CBD (Kogan et al., 2018). At the same time, the survey revealed that 30 % of US veterinarians felt uncomfortable discussing CBD use with dog owners (Kogan et al., 2018).

This review will provide an overview about the current state of knowledge regarding antiseizure effects of CBD and the application of CBD in dogs with epilepsy. Along this line, we will describe the information gaps and emphasize the need for further research and studies assessing the efficacy and safety in larger canine patient populations and providing an optimized basis for evidence-based dosing regimens.

Cannabis and phytocannabinoids

Cannabis sativa is a plant of the Cannabis genus. The plant contains numerous (> 100) phytocannabinoids (Amin and Ali, 2019). Among these, cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC) are

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the best characterized. Concerning the medical use of cannabis-based products, it is important to consider that phytocannabinoids including CBD and Δ9-THC largely differ regarding their pharmacodynamics and kinetics (Lucas et al., 2018; Alves et al., 2020). Thus, differences in bioavailability, pharmacological effects, and tolerability must be considered when selecting a cannabis-based product for a particular indication.

For Δ9-THC, which acts as a partial agonist at cannabinoid-1 (CB1) receptors and interacts with further receptors, various effects have been described with a varying level of evidence (Maida and Daeninck, 2016; Dos Santos et al., 2021; Spanagel and Bilbao, 2021). While some of these indications might also be of interest for veterinary patients, it needs to be considered that veterinary use of Δ9-THC is restricted by law in several countries. Even more importantly, in the context of therapeutic epilepsy management, it is emphasized that experimental and clinical data from human patients do not support consistent and reliable therapeutic effects of Δ9-THC on epileptic seizure development (Rosenberg et al., 2017). Based on the current state of knowledge and the described contradictory proconvulsant or anticonvulsant effects, the clinical use of Δ9-THC in patients with epilepsy is not recommended. In this context, it is of additional interest that studies analyzing the consequences of recreational use during adolescence revealed that Δ9-THC can exert long-lasting detrimental effects on brain development with consequences for cognition and the risk of psychiatric disorders (Bara et al., 2021). Although one cannot exclude the possibility that there are species differences in sensitivity of the developing brain to the effects of Δ9-THC, the corresponding experimental and clinical results from rodent models and human patients (Bara et al., 2021; Augustin and Lovinger, 2022) suggest that exposure to Δ9-THC should be avoided in young dogs.

Thus, considering legal aspects and tolerability issues, it is strongly recommended to carefully check the Δ9-THC content in cannabis-derived CBD preparations. The relevance of this recommendation is further supported by case reports from human medicine reporting epileptic seizure worsening, ataxia and behavioral alterations in pediatric patients receiving CBD-enriched cannabis extracts with approximately 3–4 % Δ9-THC content (Crippa et al., 2016). In veterinary medicine, accidental Δ9-THC ingestion can be a cause of intoxications in dogs (Henney and Coleman, 1984; Fitzgerald et al., 2013; Kelmer et al., 2019). The symptoms of a Δ9-THC intoxication can comprise behavioral alterations with lethargy, vomiting, diarrhea, bradycardia, hypothermia, muscle tremor, and ataxia. In this context, it is of interest, that dogs seem to have a lower sensitivity to proconvulsant effects of Δ9-THC than rats (Whalley et al., 2019).

As further discussed in detail below CBD has a different pharmacological profile. In contrast to Δ9-THC, CBD is not considered psychoactive. Pharmacological effects of CBD include a neuroprotective, anti-inflammatory, analgesic, anxiolytic, antiemetic, muscle relaxing, spasmolytic, sedative, tumor growth inhibition, and an anticonvulsant effect (Maida and Daeninck, 2016; Perucca, 2017; Dos Santos et al., 2021). Thereby, the level of experimental and clinical evidence for these effects differs tremendously.

Mechanism of action of CBD

Comprehensive lists of possible CBD targets and interaction partners have been published (Perucca, 2017). In this context, it is emphasized that the current state of knowledge argues against a functional relevance of the endocannabinoid receptors CB1 and CB2 for the anticonvulsant effects of CBD (Gray and Whalley, 2020).

So far, the exact mechanisms of epileptic seizure control by CBD have not been elucidated in veterinary or human patients. However, experimental research has focused on three possible targets, which might be relevant for the antiseizure effects of CBD (Fig. 1). Intracellular calcium concentrations have a major impact on release of neurotransmitters from presynaptic vesicles, and can, therefore, influence excitability in a relevant manner (Katz and Miledi, 1967). In line with this key role of intracellular calcium for hyperexcitability, two of the suggested CBD targets seem to lower intracellular calcium concentrations. The first is the orphan G protein-coupled receptor-55 (GPR55) that can mediate a rise in intracellular calcium concentrations and modulates gene expression patterns (Marichal-Cancino et al., 2017; Gray and Whalley, 2020). Cannabidiol seems to act as an antagonist of GPR55 (Gray and Whalley, 2020). Evidence for the role of GPR55 interaction as a mechanism for the antiseizure effects of CBD came from experiments demonstrating that genetic deletion limits the anticonvulsant effects of CBD in an acute seizure model (Bazelot and Whalley, 2016). Moreover, CBD did not exert further effects on isolated neurons that were pre-exposed to another GPR55 antagonist (Kaplan et al., 2017).

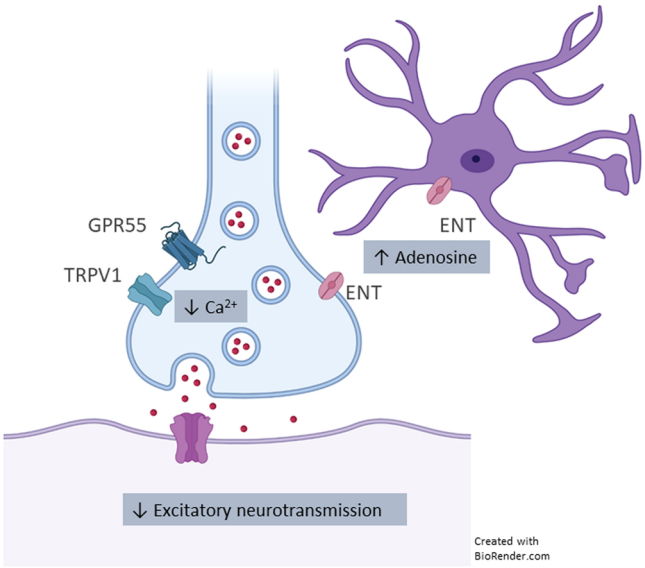

Fig. 1. Proposed mechanisms of cannabidiol's (CBD's) anticonvulsant effects. It has been suggested that CBD can limit neuronal excitability based on a reduction of presynaptic intracellular calcium concentrations, which in turn prevents excessive neurotransmitter release (Gray and Whalley, 2020). Experimental evidence suggests that these effects on calcium concentrations may be mediated by a functional antagonism at G protein-coupled receptor 55 (GPR55) receptors and a desensitization of transient receptor potential vanilloid 1 (TRPV1) receptors. In addition, an impact of CBD on extracellular adenosine concentrations has been proposed as a mechanism of action (Gray and Whalley, 2020). Adenosine can act as an endogenous anticonvulsant contributing to seizure termination. This effect of adenosine has been proposed to be mediated by an impact on calcium and potassium fluxes, which on one hand can affect presynaptic neurotransmitter release and on the other hand can contribute to postsynaptic hyperpolarization resulting in a reduced activation of glutamatergic NMDA receptors (Purnell et al., 2021). Figure created using commercially available software .[11] ENT, Equilibrative Nucleoside Transporter.

The second target candidate is the transient receptor potential vanilloid-1 (TRPV1), which mediates an influx of sodium and calcium, and can thereby enhance synaptic activity (Gray and Whalley, 2020; Seebohm and Schreiber, 2021). Cannabidiol can act as a TRPV1 agonist, which triggers a rapid desensitization, resulting in a limitation and downregulation of TRPV1-mediated signaling and activity (Bisogno et al., 2001; De Petrocellis et al., 2011). Recently, Gray and colleagues (2020) reported that the anticonvulsant effect of CBD in an acute seizure model is limited in TRPV1 knockout mice with an obvious shift in the dose-response curve related to the genetic deficiency. These data suggest that the interaction with TRPV1 is crucial for CBD's antiseizure effects. On the other hand, a recent study in a genetic mouse model of Dravet syndrome, which is one of the main indications for CBD, rather argued against a relevant influence of pharmacological or genetic modulation of TRPV1 (Janve et al., 2021), thus, raising doubts about the role of TRPV1 as a relevant target for CBD as an antiseizure medication (ASM). As

further described below, Dravet syndrome is a severe developmental and epileptic encephalopathy often caused by a genetic SCN1A variant resulting in an interneuron dysfunction (Cardenal-Munoz et al., 2022).

The third candidate mechanism is an inhibition of adenosine reuptake. It is well known that a reduction in extracellular adenosine can contribute to the development of epilepsy and that increasing its levels can exert anticonvulsant effects with relevance for endogenous seizure termination (Beamer et al., 2021). Respective observation reflect findings suggesting that reduced adenosine is one factor that can contribute to epilepsy development.

Experimental evidence supports an impact of CBD on adenosine-mediated signaling processes (Gray and Whalley, 2020). In particular, CBD can increase extracellular concentrations of adenosine based on inhibition of cellular reuptake of purine (Liou et al., 2008; Mijangos-Moreno et al., 2014; Gray and Whalley, 2020). Thus, it has been suggested that the inhibition of adenosine transport and associated enhancement of adenosine signaling may contribute to the antiseizure effect of CBD (Gray and Whalley, 2020).

Further mechanisms of action have been discussed in the context of CBD use for therapeutic management of epilepsies. Whereas some would be plausible targets for antiseizure effects, there is a lack of information for a relevant interaction and contribution at therapeutic concentrations (Gray and Whalley, 2020). Thus, more research is obviously required to determine the precise mechanism of action of CBD. In this context, it would be of particular interest to address the question of whether an interference with glial cell function and proinflammatory signaling (for review see: Scarante et al., 2020) contributes to CBD's antiseizure effects or might even mediate disease-modifying effects. Moreover, it would be of interest to further assess the potential role of an interaction of CBD with mechanistic target of rapamycin (mTOR) signaling, which has recently been suggested as a potential target with relevance for CBD's anticonvulsant effects (Lima et al., 2020). In addition, the proposed interaction of CBD with voltage-gated sodium channels (Ghovanloo et al., 2018) should be further explored. While modulators of voltage-gated sodium channels with an impact on transient sodium currents can exert proconvulsant effects in certain etiologies (e.g., in patients with Dravet syndrome), they are first line ASMs in human medicine for various types of epilepsies.

Pharmacokinetics of CBD in dogs

The oral bioavailability of CBD has been reported to be low in humans and dogs ranging from 6 % to < 19 %, respectively (Samara et al., 1988). The compound has low aqueous solubility and undergoes a high first-pass effect through the liver (Samara et al., 1988). Absorption may also be influenced by aspects related to the product and pharmaceutical formulation, gastrointestinal tissue integritry, and the volume administered (Samara et al., 1988; Deabold et al., 2019; Verrico et al., 2020; Wakshlag et al., 2020). To enhance oral bioavailability and due to their highly lipophilic nature, cannabinoids are often administered in oil-based formulations (Zgair et al., 2016). Bartner et al. (2018) determined the pharmacokinetic profile of CBD in healthy dogs given one of three formulations (oral microencapsulated oil beads, oral CBD-infused oil, or CBD-infused transdermal cream) during a 6-week study period. Serial CBD plasma concentrations were measured over time and the highest plasma concentrations were observed with the oral CBD-infused oil formulation, which was associated with the most favorable pharmacokinetic profile. In rats, oral co-administration of lipids enhanced the plasma concentrations of THC and CBD by 2.5-fold and 3-fold, respectively, compared to lipid-free formulations (Zgair et al., 2016). The feeding status of animals is likely to be important, as administration of lipophilic CBD/THC-based formulations to humans in the fed state (particularly with high-fat meals) resulted in a significantly higher CBD bioavailability than during fasting conditions (Chicoine et al., 2020; Birnbaum et al., 2019). Conversely, a high-THC formulation had lower bioavailability when administered in the fed vs. fasting state in a small number of dogs (Lebkowska-Wieruszewska et al., 2018). If owners choose to administer CBD/THC-based products to their dogs, veterinary recommendations should include consistent administration of these products relative to a meal (fed or fasting). This will minimize the potential for large changes in cannabinoid exposure with repeated dosing, thus minimizing possible inefficacy or toxicity due to decreased or increased exposure, respectively.

Most hemp-based products intended for use in dogs are currently being administered orally, aimed primarily at the practicability for the owner. However, the search for alternative delivery routes is needed to achieve successful therapeutic effects by circumventing the hepatic first-pass effect. Administration of CBD has been reported rectally, transdermally, intranasally, through the orotransmucosal route (e.g., sublingual) and by inhalation in humans (Bruni et al., 2018). In dogs, the pharmacokinetics of cannabinoids have been evaluated in studies involving the administration of different doses of Δ9-THC, CBD, or products containing both phytocannbinoids by transdermal, intravenous, and sublingual routes (Samara et al., 1988; Bartner et al., 2018; Gamble et al., 2018; Deabold et al., 2019; Chicoine et al., 2020; Fernandez-Trapero et al., 2020; Hannon et al., 2020). A study in healthy dogs by Polidoro et al. (2022) analyzed the pharmacokinetic profile of CBD after oral, intranasal and rectal administration and showed a favorable profile for the oral route.

It is important to acknowledge or identify potential pharmacokinetic interactions between the pharmaceutical formulation of CBD and the commonly used ASMs (Gaston et al., 2017; Gilmartin et al., 2021). The cytochrome p450 (CYP) system in particular has been implicated in pharmacokinetic interactions. Cannabidiol is metabolized by the CYP system in the liver and inhibits several CYP-isoenzymes, so CBD could affect the metabolism of certain ASMs (Gaston et al., 2017; Morrison et al., 2019; Gilmartin et al., 2021). There are only few studies investigating the effect of ASMs on the pharmacokinetics of CBD. Furthermore, the evidence base for some ASM interactions is quite limited (e.g. small sample size, variable trial durations). Pharmacodynamic interactions have been noticed between CBD and clobazam, valproate and levetiracetam, and there are reports of pharmacokinetic interactions for brivaracetam, clobazam, eslicarbazepine, lacosamide, gabapentin, oxcarbazepine, phenobarbital, potassium bromide, pregabalin, rufinamide, sirolimus/everolimus, stiripentol, tiagabine, topiramate and zonisamide (Geffrey et al., 2015; Klotz et al., 2019; Morrison et al., 2019). These interactions do not all affect therapeutic efficacy. McGrath et al. (2019) showed no significant change in serum phenobarbital and bromide concentrations in dogs following CBD treatment arguing against any relevant pharmacokinetic drug interaction in this study. Similarly, Doran et al. (2022) found a lack of significant pharmacokinetic interaction between CBD and phenobarbital. Therefore, the authors concluded that adjustment of the CBD dose with chronic co-administration of phenobarbital does not appear to be indicated. Also, based on the single-dose administration with CBD, adjusting the dose of phenobarbital does not appear indicated (Doran et al., 2022). However, larger studies are required to determine how these interactions influence clinical practice. As the evidence is currently limited for a number of ASMs, veterinarians should carefully monitor both clinical and laboratory parameters when introducing or changing CBD dosage, whichever ASM the dog is receiving. Until now, a low potential for clinically relevant drug-drug interactions between CBD and other ASMs has been found. A well characterized example is the interaction with clobazam and its active metabolite N-desmethylclobazam (Patsalos et al., 2020).

[1] See: Biorender. https://biorender.com (Accessed 3 October 2022).

Antiseizure effects of CBD

Human trials

In human medicine, placebo-controlled, randomized trials have been conducted in patients with three different epileptic and developmental encephalopathies (Johannessen Landmark et al., 2021), all characterized by difficult-to-treat seizures with a high rate of drug resistance. In the majority of patients Dravet syndrome is caused by a variant of the SCN1A gene resulting in an interneuron dysfunction, which is associated with a high seizure burden with different seizure types, a high risk of sudden unexpected death in epilepsy, and an impairment of cognitive and motor function (Cardenal-Munoz et al., 2022). In patients with Dravet syndrome CBD resulted in a 39 % reduction in the frequency of convulsive seizures (Devinsky et al., 2017). Lennox-Gastaut syndrome is another severe epileptic encephalopathy, which can be symptomatic and is characterized by multiple seizure types, electroencephalographic slow spike-wave complexes, and cognitive impairment (Arzimanoglou et al., 2009). In patients with Lennox-Gastaut syndrome, CBD administration resulted in a significant decrease in drop seizures (Laux et al., 2019; Thiele et al., 2019). Moreover, first data have been presented for tuberous sclerosis describing a significant decrease in focal and generalized seizures as a consequence of CBD administration (Thiele et al., 2019; Johannessen Landmark et al., 2021). Case reports and open-label studies provide first low-level evidence that CBD might also be efficacious in other epilepsy syndromes (Johannessen Landmark et al., 2021). Taken together, clinical data from human patients support a relevant antiseizure effect with efficacy against various seizure types. Thus, while ancient reports have already suggested the clinical use of cannabis-based products in patients with seizures, convincing evidence from controlled trials with CBD in human patients with epileptic encephalopathies has only recently become available.

Seizure and epilepsy models

An anticonvulsant effect of CBD has also been demonstrated in various acute seizure models including the traditional screening models, i.e. the maximum electroshock seizure test and the pentylenetetrazole test. An assessment of CBD in the epilepsy therapy screening project of the National Institute of Neurological disorders and stroke (NINDS) confirmed these findings and additionally demonstrated effects of CBD in the 6 Hz 44 mA mouse model, an acute seizure model in mice with poor responsiveness to various ASMs, and in a chronic mouse model with repeated electrical induction of seizures. Taken together, experimental testing confirmed relevant antiseizure effects against focal onset and generalized epileptic seizures at well tolerated doses (Klein et al., 2017). Experimental and clinical data have motivated scientists to assess CBD's efficacy in various epilepsy models (Rosenberg et al., 2017). Thereby, studies in laboratory mice revealed a relevant effect in models of Dravet syndrome, a severe epileptic and developmental encephalopathy with a poor pharmacoresponse (Kaplan et al., 2017; Anderson et al., 2019). Moreover, activity against non-convulsive seizures was suggested by findings from genetic absence epilepsy rats from Strasbourg (Roebuck et al., 2021).

Drug-refractory canine epilepsy

One randomized masked controlled clinical trial has been completed assessing the efficacy of CBD in canine patients with drug-refractory epilepsy (McGrath et al., 2019). Among others, the inclusion criteria comprised: 1) a tier II confidence level for diagnosis of idiopathic epilepsy according to the IVETF consensus proposal by Berendt and colleagues (2015); 2) at least two epileptic seizures per month for a minimum of 16 weeks; 3) treatment with at least one conventional ASM; and 4) phenobarbital or potassium bromide concentrations in the therapeutic range and/or administration of zonisamide or levetiracetam at recommended doses (McGrath et al., 2019). The majority of the dogs received a polytherapy with a combination of at least two ASMs. The ASM treatment protocol was supposed to be continued without dose adjustment throughout the study duration. Twenty-six dogs with drug-refractory idiopathic epilepsy were successfully enrolled in the study. These dogs were randomly allocated to a group receiving CBD-infused oil with twice daily oral administration of 2.5 mg/kg CBD ($n = 12$) and a placebo group receiving the same oil without CBD ($n = 14$). Unfortunately, there was a high number of dropouts with only seventeen (CBD group $n = 9$ and placebo group $n = 8$) of the 26 dogs completing the study (McGrath et al., 2019). Withdrawal was related to ASM adjustments ($n = 3$ from the placebo group), difficulties of owners to show up at the scheduled appointments ($n = 3$ from the placebo group), euthanasia due to status epilepticus ($n = 1$ from CBD group), and general proprioceptive ataxia as a possible adverse effect in two dogs from the CBD-treated group. Another dog from the placebo group had to be excluded from the analysis as the owner had initiated an administration of CBD-infused oil during the final month of the study. Overall, six dogs in the placebo group withdrew from the study (owner compliance issues) and three dogs in the CBD group withdrew (euthanasia due to seizure activity [$n = 1$] and ataxia [$n = 2$]).

Seizure data from the 16 weeks before initiation of the study were considered as baseline data for comparison with the study phase. While the mean monthly seizure frequency was not affected in the placebo group, a 33 % reduction became evident in CBD-treated dogs. While these findings might indicate an antiseizure effect of CBD, the number of responders with an at least 50 % reduction in seizure frequency proved to be identical in both dog groups. Plasma concentrations of CBD were repeatedly analyzed 4, 8 and 12 weeks following initiation of the study. Interestingly, a negative correlation was confirmed between the percentage change in seizure frequency and CBD plasma levels (McGrath et al., 2019). The authors concluded that follow-up studies are required to assess the efficacy of CBD in larger populations of canine patients with idiopathic epilepsy as a basis for robust conclusions. Moreover, they discussed whether higher doses might be necessary to achieve relevant therapeutic effects. In this context, it is important to consider that in general clinical use of ASMs is based on an individual titration to an efficacious dose if necessary up to the maximum tolerated dose. This is in contrast to fixed dose protocols often applied in clinical studies, including the study focusing on CBD in canine idiopathic epilepsy (McGrath et al., 2019).

In a recent article focusing on the question of whether adding CBD to conventional ASMs has beneficial effects in dogs with epilepsy, Morrow and Belshaw (2020) came to the conclusion that data from larger-scale studies with a longer study duration are necessary to answer this question. In this summary, they also emphasized that in addition to the limited sample size and evidence for baseline differences between groups, the specific characteristics of the CBD-infused hemp oil product used in the study by McGrath and colleagues (2019) needs to be considered. Moreover, Morrow and Belshaw (2020) suggested that conclusions might have been limited, related to the focus on monthly mean seizure frequencies and the fact that multiple epileptic seizures during a 24 h period were considered as one seizure episode.

More recently, findings from another randomized masked clinical trial in fourteen dogs with idiopathic (IVETF level II confidence) or presumed idiopathic epilepsy (IVETF level I confidence) were published (Garcia et al., 2022). This trial was based on a cross-over design with dogs receiving placebo or CBD/cannabidiolic acid (CBDA)-rich hemp extract in a sesame oil preparation. Treatment was switched after 3 months. During CBD/CBDA exposure, seizure frequency as well as the number of days with seizure activity were significantly lower than during the placebo phase (Garcia et al., 2022). The number of responders with a $\geq$ 50 % reduction in seizure frequency amounted to six of 14 dogs in the CBD/CBDA treatment phase, whereas a respective reduction was not observed while dogs were on placebo. Except for mild increases in alkaline phosphatase, no changes in blood counts and serum

chemistry became evident. Moreover, the data argued against a relevant impact on serum concentrations of phenobarbital, zonisamide, and bromide. In line with previous reports, adverse events were minor with somnolence and ataxia observed in three and four dogs, respectively (Garcia et al., 2022).

Future directions

In future studies it would be of additional interest to assess the impact of CBD on behavioral comorbidities and cognitive dysfunction in dogs with epilepsy. Preclinical data suggest that CBD can exert anxiolytic and antidepressant effects, and can attenuate cognitive dysfunction in laboratory rodents (for detailed reviews see Gaston et al., 2021; Melas et al., 2021). However, experimental evidence exists that the effects depend on influencing factors with a pronounced effect of treatment duration. The latter can even result in a reversal of effects with an anxiogenic effect of chronic CBD exposure in rats (ElBatsh et al., 2012). Moreover, a recent controlled trial in human patients with anxiety disorders did not confirm CBD as an efficacious adjunctive therapy (Kwee et al., 2022). Further preclinical and clinical research seems to be necessary to determine the potential of CBD as a treatment option for epilepsy-associated psychiatric comorbidities and cognitive dysfunction.

Tolerability of CBD and CBD products in dogs

Randomized, masked, controlled trials and open label extension trials in human patients with developmental and epileptic encephalopathies confirmed an acceptable safety profile of CBD. The most common adverse effects comprised diarrhea, pyrexia, decreased appetite and somnolence (e.g. Devinsky et al., 2017; Scheffer et al., 2021; Patel et al., 2021).

Safety and tolerability of the application of CBD-containing oil was assessed in healthy dogs and in studies evaluating the treatment of canine osteoarthritis pain. An experimental study with dose escalation of CBD and Δ9-THC confirmed a better tolerability of CBD vs. Δ9-THC. After the application of a CBD-predominant oil and giving up to ten escalating doses up to the tenth dose (about 62 mg/kg) adverse events (AEs) were reported (Vaughn et al., 2020). The majority of AEs were considered to be mild and included gastrointestinal (nausea, emesis, diarrhoea), constitutional (apathy, hyperesthesia) or neurological (muscle tremor, ataxia) signs (Vaughn et al., 2020). Respiratory, dermatological and ocular changes were rare (Vaughn et al., 2020). Blood analysis revealed an elevation of alkaline phosphatase (Vaughn et al., 2020). A recent study of this group reported hypersalivation, lip-licking, vomiting, loose feces and dehydration following application of high CBD dosages (12 mg/kg) (Vaughn et al., 2021). Elevation of serum alkaline phosphatase (ALP) values was confirmed, but no other concomitant increase of hepatic markers was found (Vaughn et al., 2021).

A study evaluating twice daily application of chews with 2 mg/kg of a 50:50 mix of CBD and CBDA for 84 days to healthy adult dogs confirmed that this treatment regime appears to be safe with only mild gastrointestinal signs (Deabold et al., 2019). Hematology and biochemistry parameters remained in the reference range. Interestingly, the authors describe more pronounced AEs in healthy cats with licking, head shaking, pacing, chewing and gagging (Deabold et al., 2019). Tolerability studies were also assessed in dogs with osteoarthritis exposed to 2 mg/kg CBD every 12 h. While one of the studies assessing 2 mg/kg every 12 h confirmed an increase of ALP values (Gamble et al., 2018), the other study did not detect significant alterations (Verrico et al., 2020). In the latter study, the exact dosage of CBD in mg/kg was not provided (Verrico et al., 2020). In dogs with idiopathic epilepsy, an ALP increase was observed in the CBD group (McGrath et al., 2019).

In another study in healthy Beagle dogs, the application of a 1:20 THC:CBD cannabis herbal extract resulted in neurological signs, when high dosages (CBD 10 mg/kg bodyweight) were administered (Chicoine et al., 2020). Signs included hyperesthesia (overreaction to normal auditory/visual/tactile stimuli), proprioceptive deficits, head bobbing, torso swaying, ptyalism, urinary incontinence and vomiting (Chicoine et al., 2020). The application of lower dosages (2 mg/kg and 5 mg/kg) resulted in mild neurological deficits such as mydriasis, ataxia, delayed hopping reaction and noise sensitivity in a few dogs (Chicoine et al., 2020). Blood counts and biochemistry values remained in reference ranges.

While clinical studies assessing the efficacy of CBD in canine idiopathic epilepsy or osteoarthritis did not report severe adverse events, one case report provided the first evidence that in rare cases severe adverse reactions may be possible as a consequence of treatment with a CBD-containing hemp oil. Five days after initiation of the administration, a 4-year old Labrador Retriever developed a severe cutaneous adverse drug reaction with clinical signs reflecting those of Stevens-Johnson syndrome in human patients (Simpson et al., 2020). The signs comprised diarrhoea, anorexia, lethargy, and wide-spread cutaneous and mucosal ulceration (Simpson et al., 2020). Discontinuation of the administration of the CBD-containing hemp oil resulted in a complete resolution of all clinical signs over time. The authors concluded that a link with the exposure to the oil is considered probable in this case (Simpson et al., 2020). However, as also emphasized by the authors, the case report does not allow any conclusions concerning a possible risk associated with CBD exposure as the hemp oil preparation contains various components including other cannabinoids, terpenoids, and coconut oil as a carrier (Simpson et al., 2020).

In this context, it is of interest that a US study that analyzed 29 products with low-THC Cannabis sativa extracts suggested a poor quality of many products (Wakshlag et al., 2020). Cannabidiol concentrations proved to be highly variable with only 18 products appropriately labeled and no detectable CBD in two products (Wakshlag et al., 2020). In four products, heavy metal contaminations were identified in this analytical study. Along this line an earlier study focused on cannabidiol extracts sold online for human use revealed major labeling inaccuracies (Bonn-Miller et al., 2017). In this study only 31 % of 84 CBD products were accurately labeled, while 43 % were underlabeled amd 26 % were overlabeled. In this context, it is emphasized that some of these products are marketed with a pharmaceutical grade label. These findings point to the particular relevance of licensed controlled pharmaceuticals, when it comes to testing and application of CBD.

Future perspectives

While there is convincing proof for relevant anticonvulsant effects from both rodent models and human patients with epilepsy, there is an obvious need to conduct large-scale randomized controlled trials in canine patients to further evaluate the efficacy in canine idiopathic epilepsy. Multicenter approaches might thereby contribute to a high level of reproducibility and generalizability allowing robust conclusions about the therapeutic potential. In the long-run, this may also allow conclusions about the efficacy in patients with different etiologies, epilepsy types, severity and duration of seizures (e.g. single generalized seizures, cluster seizures or status epilepticus), and in dogs of various breeds.

In this context, further efforts should be made to provide a basis for evidence-based dosing regimens also considering the temporal association with feeding and the type of food. Considering the high variation in plasma concentrations following administration of CBD preparations, it will also be necessary to determine the range of therapeutic plasma concentrations in dogs. Respective information will also be of particular value considering the pronounced influence of the pharmaceutical formulation of the CBD preparations on oral bioavailability.

Subgroup analysis in large-scale clinical studies can provide information about additive, synergistic or antagonistic effects of combinations between CBD and other ASMs. This may provide guidance for

rational polytherapy with CBD. While available data for CBD and phenobarbital or potassium bromide argue against a relevant pharmacokinetic interaction (McGrath et al., 2019; Doran et al., 2022), future clinical research should in more detail assess the pharmacokinetic interaction potential with different ASMs used in dogs.

While it is evident that higher Δ9-THC concentrations should be avoided in patients with epilepsy, possible 'entourage' effects cannot be excluded with other components in cannabis extracts including various phytocannabinoids and terpenes. Thus, there is an urgent need to continue with studies exploring the pharmacological effects of different cannabis components.

Conclusions

Available data from other species, including human patients, suggests that it is likely that CBD can exert anticonvulsant effects in dogs. Up to now, clinical data from controlled trials are limited to two trials in canine patients with drug-refractory idiopathic epilepsy. Further efforts are necessary to determine the range of therapeutic plasma concentrations and to develop optimized dosing regimens. In this context, the influence of the formulation and of feeding needs to be taken into account. Based on the current state of knowledge, it still remains impossible to provide definite clear-cut recommendations for the use of CBD in dogs with drug-refractory epilepsy. For individual therapy attempts, it is recommended to consider the pharmaceutical quality of the CBD formulation, to avoid CBD formulations with > 0.2 % Δ9-THC, and to closely monitor ALP levels. Moreover, it needs to be taken into account that dose titration is limited as doses of 10 mg/kg CBD can be associated with unacceptable adverse effects in dogs.

Conflict of interest statement

HP has received funding for consulting, talks and research collaborations from Eisai, Zogenix, Elanco, Roche, Lario/Exeed Epidarex, Angelini, Jazz Pharmaceuticals and MSD. SM has received funding for consulting, talks and research collaborations from Applied Basic Science Corporation and Canopy Growth Corporation. AT received funding for research collaborations by Boehringer Ingelheim. The authors have no other financial or personal relationships with other people or organisations that could inappropriately influence or bias the content of the paper.

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