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Review

Non-pharmacological treatment options for refractory epilepsy: An overview of human treatment modalities and their potential utility in dogs

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ABSTRACT

Refractory epilepsy is a common disorder both in humans and dogs and treatment protocols are difficult to optimise. In humans, different non-pharmacological treatment modalities currently available include surgery, the ketogenic diet and neurostimulation. Surgery leads to freedom from seizures in 50–75% of patients, but requires strict patient selection. The ketogenic diet is indicated in severe childhood epilepsies, but efficacy is limited and long-term compliance can be problematic. In the past decade, various types of neurostimulation have emerged as promising treatment modalities for humans with refractory epilepsy. Currently, none of these treatment options are used in routine daily clinical practice to treat dogs with the condition. Since many dogs with poorly controlled seizures do not survive, the search for alternative treatment options for canine refractory epilepsy should be prioritised. This review provides an overview of non-pharmacological treatment options for human refractory epilepsy. The current knowledge and limitations of these treatments in canine refractory epilepsy is also discussed.

Introduction

Epilepsy is one of the most common chronic neurological disorders both in humans (Sander and Shorvon, 1996; Brodie et al., 1997) and dogs (Bielfelt et al., 1971; Cunningham and Farnbach, 1988; Schwartz-Porsche, 1994; Knowles, 1998). Most dogs have idiopathic epilepsy (Schwartz-Porsche, 1994; Jaggy and Bernardini, 1998) and they are often managed successfully with standard antiepileptic drugs (AEDs; Schwartz-Porsche et al., 1985; Schwartz-Porsche and Jurgens, 1991), but approximately 30% of cases are refractory to treatment (Lane and Bunch, 1990). Interestingly, the prevalence of refractory epilepsy is similar in humans (Kwan and Brodie, 2000). Unfortunately, although a substantial number of new AEDs have become available (Beghi, 2004), several long-term studies have demonstrated that few human patients became seizure free after initiating a third AED when two AEDs have failed (Kwan and Brodie, 2000; Mohanraj and Brodie, 2005, 2006). Therefore, non-pharmacological treatment options are becoming increasingly important in humans.

Only a limited number of the newer treatment strategies in humans have been investigated in canine epilepsy. Currently, many dogs with refractory epilepsy are eventually euthanased or die during uncontrollable seizures (Arrol et al., 2012; Monteiro et al., 2012).

Dietary treatment of refractory epilepsy

The ketogenic diet and human epilepsy

The antiepileptic effect of fasting was noted almost 100 years ago (Geyelin, 1921) and the ketogenic diet (KD) was introduced in that same year for the treatment of epilepsy (Wilder, 1921). Over the next 20 years, the KD became a popular treatment for both children and adults with epilepsy, but with the development of different AEDs, the popularity and use of the KD diminished (Kossoff et al., 2009a). A renewed interest and research into the efficacy of the KD was initiated around 1994, due to the successful treatment of the refractory seizures of a famous American film producer's son (Kossoff et al., 2009a). This diet is used mainly for the treatment of refractory childhood epilepsy (Kossoff et al., 2009b) and is high in fat (80%), low in carbohydrates (5%) and has adequate amounts of protein (15%), based on minimum daily requirements (Kossof, 2004). The classic KD is also called the 'long-chain triglyceride' diet or the '4:1 fat:non-fat' diet (Kossoff et al., 2009a).

Despite much in vitro and in vivo investigation, the precise antiepileptic mechanism of action (MOA) of the KD still remains unknown (Schwartzkroin, 1999; McNally and Hartman, 2012). It

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has been suggested that elevated concentrations of ketone bodies are primarily responsible for the anticonvulsant effects of the KD, perhaps by altering the energy metabolism in the brain, changing neuronal properties (by altering ion channels, the neuronal membrane potential or the cell membrane composition), inhibiting the production of reactive oxygen species and/or inducing a mild reduction of brain pH. Ketone bodies might also affect the concentrations and function of neurotransmitters and their receptor activity (Schwartzkroin, 1999; McNally and Hartman, 2012). The paediatric brain extracts and uses ketone bodies from the blood more efficiently due to higher levels of ketone metabolising enzymes and monocarboxylic acid transporters; this could explain why the diet seems to be more efficacious in children than in adults (Sokoloff, 1973; Bilger and Nehlig, 1992).

Clinical trials have demonstrated that approximately 50% of children with refractory seizures who receive the KD will have at least 50% reduction in seizures. Furthermore, a decrease in seizure frequency of $\geqslant$90% is achieved in about one-third of patients (Henderson et al., 2006; Neal et al., 2008; Kossoff et al., 2009a; Kessler et al., 2011). It should be remembered that these apparently impressive outcomes were not generated by randomised, controlled trials (Neal and Cross, 2010; Levy et al., 2012).

The ketogenic diet and canine epilepsy

Only one abstract describes the use of a KD in dogs with refractory idiopathic epilepsy (Patterson et al., 2005). Dogs receiving the ketogenic food over a period of 6 months had significantly higher serum ketones than controls, but there was no significant difference in seizure frequency between the groups. Since this could result from lack of statistical power due to small sample size, this treatment might deserve further investigation in larger studies, since dietary change should be achievable by compliant dog owners. However, it is more difficult to induce ketosis by starvation in dogs than in humans (Crandall, 1941). The level of ketosis achieved in the study by Patterson et al. (2005) seems low compared to effective concentrations of ketones in children receiving the KD. Additionally, canine epilepsy might be different to the type of epilepsy experienced by people who respond to the diet.

Essential fatty acid supplementation and human epilepsy

Dietary omega-3 (ω-3) and omega-6 (ω-6) polyunsaturated fatty acids (PUFAs) are involved in many physiological processes in the brain. It is thought that ω-3 PUFAs could have anticonvulsant effects through mechanisms explained elsewhere (Taha et al., 2010). Docosahexaenoic acid (DHA), the primary ω-3 PUFA in the brain, is an important structural part of the neuronal membrane and the most commonly accepted hypothesis to explain its possible anticonvulsant MOA is that it modulates ion channels, mainly voltage-dependent sodium channels. PUFAs might also raise the seizure threshold by activating peroxisome proliferator-activated receptors or by antagonizing neuroinflammation (Taha et al., 2010). Recent evidence from in vitro and animal studies suggests that ω-3 PUFAs could have a potential use in the treatment of epilepsy (Taha et al., 2010), although conflicting results have been found in human clinical studies (Schlanger et al., 2002; Yuen et al., 2005; Bromfield et al., 2008; DeGiorgio et al., 2008).

Essential fatty acid supplementation and canine epilepsy

A case report about the positive effect of daily supplementation with fish oil, a rich source of PUFAs, on seizure frequency in a Great Dane with idiopathic epilepsy has been described (Scorza et al., 2009). More recently, a single-blinded, placebo controlled cross-over trial investigated the effects of ω-3 oil supplementation on seizure frequency and severity in 15 dogs with idiopathic epilepsy (Matthews et al., 2012). No significant difference in seizure frequency and severity was found between the treatment and placebo period, but the study had low statistical power.

Surgical treatment of refractory epilepsy

In human patients with a well-defined focal seizure onset, surgery is the treatment of choice when at least two AEDs have proven insufficient for control. Selection criteria for surgery can differ between centres, leading to a lack of standardised approach (Ryvlin and Rheims, 2008). Because of the concern that recurrent seizures could have harmful effects on the brain, early surgical intervention is now more often recommended, especially in children with focal epilepsies and adults with temporal lobe epilepsy (TLE; Noachtar and Borggraefe, 2009). However, the evidence to support early surgical intervention is indirect and incomplete (Langfitt and Wiebe, 2008). There are two major categories of epilepsy surgeries: curative or resective surgeries and palliative or disconnective surgeries (Kunieda et al., 2012).

Resective surgery

Resective techniques are more commonly performed than disconnective surgeries and are mainly beneficial in patients with focal onset seizures. The goal of resective surgery is to eliminate seizures completely and to improve cognitive and psychosocial outcomes without causing substantial neurological deficits. Theoretically, this can be achieved by resecting the epileptogenic focus without damaging healthy cortical tissue. Outcomes depend on the completeness of removal of the epileptogenic tissue and the avoidance of resection of eloquent cortex (Awad et al., 1991). Unfortunately, the localisation of the epileptogenic focus is not always possible. Resective surgery can be either temporal or extra-temporal.

Temporal resections

Particularly for TLE, the advantages of surgical over medical treatment have been well documented (Wiebe et al., 2001; Engel et al., 2003; Téllez-Zenteno et al., 2005). Temporal lobectomy leads to long-term seizure control in the majority of patients with TLE and hippocampal sclerosis (Kunieda et al., 2012) and about 65% of treated patients become seizure-free (Engel et al., 2003). Consequently, this is the most commonly performed surgical technique for epilepsy in humans and outcomes have been studied extensively (Téllez-Zenteno et al., 2005). More selective partial resections such as amygdalohippocampectomies are currently performed with promising results for TLE (Wieser and Yasargil, 1982), although a critical review and meta-analysis comparing standard versus selective TLE surgery concluded that the chance of achieving freedom from seizures improves following standard resection of the temporal lobe (Josephson et al., 2013).

Extra-temporal resections

In extra-temporal cortical epilepsy, the boundaries of the epileptogenic focus are more variable, which makes it more difficult to define the limits of resection. Various long-term outcomes have been reported depending on which brain lobe was involved in the resection. In one study, 46% of patients became seizure-free after occipital and parietal resections and 27% after frontal lobe resections (Téllez-Zenteno et al., 2005).