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The role of nutrition in canine idiopathic epilepsy management: Fact or fiction?

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ABSTRACT

In the last decade, nutrition has gained interest in the management of canine idiopathic epilepsy (IE) based on growing scientific evidence. Diets can serve their functions through many pathways. One potential pathway includes the microbiota-gut-brain axis, which highlights the relationship between the brain and the intestines. Changing the brain's energy source and a number of dietary sourced anti-inflammatory and neuroprotective factors appears to be the basis for improved outcomes in IE. Selecting a diet with anti-seizure effects and avoiding risks of proconvulsant mediators as well as interference with anti-seizure drugs should all be considered in canine IE. This literature review provides information about preclinical and clinical evidence, including a systematic evaluation of the level of evidence, suggested mechanism of action and interaction with anti-seizure drugs as well as pros and cons of each potential dietary adaptation in canine IE.

Introduction

The history of using dietary regimens in the management of epilepsy in humans began in 500 BCE (Wheless, 2008). The popular quote by Hippocrates 'let thy food be thy medicine and thy medicine be thy food' sparked the interest of scientists and nutritionists to study the importance of nutrition in disease prevention and treatment. This interest is now slowly disseminating into veterinary medicine (Witkamp and van Norren, 2018) and more recently into veterinary neurology.

Idiopathic epilepsy (IE) is a common chronic neurological disease in dogs (Berendt et al., 2015) and is mainly treated with anti-seizure drugs (ASDs; Bhatti et al., 2015; Podell et al., 2016). Along with ASDs, nutrition can play an important role in the management of canine IE (Larsen et al., 2014; Han et al., 2021). Due to the assumed positive aspects of nutrition, a study in 297 owners of dogs with IE showed, that two-thirds of the owners started to change their dogs' nutrition and almost half of them added food supplements after their animals were diagnosed with IE (Berk et al., 2018). Interestingly, two out of three owners changed the diet unsupervised by a veterinary surgeon, solely based on information from the internet. Only one out of five owners asked a veterinary surgeon for advice (Berk et al., 2018). However, the selection of an appropriate diet in canine IE is essential and should be made with caution because some nutritional components could play a role in epileptic seizure development and could alter the

Abbreviations: ASDs, Antiseizure drugs; IE, Idiopathic epilepsy; MGBA, Microbiota-gut-brain axis; ENS, Enteric nervous system; CNS, Central nervous system; GIM, Gastro-intestinal microbiome; GI, Gastro-intestinal; KD, Ketogenic diet; KBs, Ketone bodies; MCTs, Medium chain triglycerides; LCFA, Long chain fatty acids; MCFA, Medium chain fatty acids; BBB, Blood-brain-barrier; GABA, Gamma-aminobutyric acid; TCA, Tricarboxylic acid; SCFA, Short chain fatty acids; SF, Seizure frequency; CBD, Cannabidiol; ALA, Linolenic acid; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; PUFAs, Polyunsaturated fatty acids; Pb, Phenobarbital; KBr, Potassium bromide.

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pharmacokinetics of ASDs (Trepanier and Babish, 1995; Maguire et al., 2000). Diet history and a better understanding of the impact of diets on IE therefore need to be considered in daily practice by clinicians, ideally in consultation with a nutritionist.

The therapeutic aims of nutrition for IE are threefold: first; sustenance for adequate brain functions; second; halt or decelerate disease progression; third; decreasing side effects of ASDs as well as alleviating behavioural comorbidities of IE. In the last decades, the action of nutrition via the microbiota-gut-brain axis (MGBA) has gained a lot of attention. The MGBA provides a bidirectional communication pathway between the gastro-intestinal tract, the enteric nervous system (ENS) and the central nervous system (CNS) via the vagal and spinal afferent nerves, immune system, the hypothalamic–pituitary–adrenal cortical axis and bacterial metabolites. An important factor in this axis is the gastrointestinal microbiome (GIM; O'Mahony et al., 2015). The microbiome refers to the collection of genomes from all the microorganisms, whereas microbiota refers to specific microorganisms in a particular environment (Suchodolski, 2022). The GIM is greatly influenced by nutrition (Coelho et al., 2018; Muñana et al., 2020). Studies show an important role of the GIM in the pathogenesis and management of epilepsy. Both human and canine studies demonstrated a different gastrointestinal (GI) microbiota composition in epileptic cases compared to healthy controls (Table 1), which supports a potential role for dysbiosis, i.e. disease-promoting imbalance in the GI microbiota composition (Weiss and Hennet, 2017), in epileptogenesis. In addition, the GIM of drug-resistant epilepsy patients was significantly altered compared to drug-sensitive patients in humans, indicating a potential role for the normalisation of the GIM towards the GIM of healthy individuals in the management of epilepsy (Peng et al., 2018; Gong et al., 2021). Moreover, a study in mice showed that the GIM is both necessary and sufficient to increase seizure threshold as a response to a ketogenic diet (Olson et al., 2018). Similarly, another preclinical study showed reinforcing effects for kindling epileptogenesis by faecal transplants from stressed to non-stressed rats, and vice versa (Medel-Matus et al., 2018).

The aim of the review is to summarise current evidence on nutritional management in canine IE, its relevant mechanisms of action and the effects of nutrition on ASDs. Therefore, an extensive literature search was performed (Fig. 1) identifying 21 relevant publications. Each study was graded with a level of evidence according to the Elsevier level of evidence hierarchy for treatment studies (Table 2).

Nutritional interventions for canine IE

Ketogenic and medium chain triglyceride-enriched diets

In the 1920 s, a ketogenic diet (KD) was often used in human medicine as treatment for drug-resistant epilepsy, but with the discovery of new medical treatment options, it became less popular (Sharma and Jain, 2014). However, despite the development of a number of new ASDs since then, the percentage of drug-resistant patients has not significantly improved (Löscher et al., 2020), so that nowadays there is an increased interest in KDs. Especially for children with epilepsy, different KDs have been established for clinical use (Martin-McGill et al., 2018; Goswami and Sharma, 2019).

The classic KD is high in fat, low in protein, low in carbohydrates (typically with ratios of 2:1–4:1 of fat: protein plus carbohydrates) which in humans causes ketosis. However, in dogs, a ketogenic state has been shown to be difficult to achieve. This is assumed to be the result of a more efficient peripheral use of ketone bodies (KBs; De Bruijne and van den Brom, 1986; Puchowicz et al., 2000). An alternative to this classic KD is dietary supplementation of medium chain triglycerides (MCTs), starting from 5.5 % on a dry matter basis, i.e. an MCT-enriched diet (MCTD). Medium chain triglycerides have six to 12 carbons compared to long chain fatty acids (LCFA) with 16–22 carbons and short chain fatty acids (SCFA) with less than six carbons. Octanoic acid (8C; caprylic acid) and decanoic acid (C10; capric acid) are most important for brain metabolism and function, especially as a source for ketogenic bodies and by providing other actions such as improvement of brain mitochondrial function (Hughes et al., 2014). In comparison to LCFA, medium chain fatty acids (MCFA) have a higher ketogenic yield, can readily cross the blood-brain-barrier (BBB) and are effectively metabolised in brain astrocytes. However, MCFA are first effectively metabolised in the liver and induce the production of KBs without the need for a high restriction in carbohydrates (St-Pierre et al.,2019; Fig. 2). This is beneficial because carbohydrates in pet food are important for their technological properties in the production of dry kibbles and as an energy source[2].

The principle of a KD and MCTD is to partly shift the energy supply of the brain from glucose (the brain's regular energy source) to KBs (Bough and Rho, 2007), as the glucose metabolism is altered in the epileptic brain (Han et al., 2021). As a result, the energy received from KBs alleviates the brain's energy deficiency by restoring about 60 % of energy demand (Owen et al., 1967). During a seizure, the brain might utilise a large amount of glucose, but in the interictal period, glucose metabolism is reduced in the brain area of the epileptic focus. This 'hypometabolic' state can also affect other brain areas, often associated with an increase in seizure frequency and severity, indicating that a change in local energy metabolism can be associated with seizure generation and propagation and be a cause for drug-resistance (Viitmaa et al., 2014). The lack of energy provided through altered and reduced glucose metabolism can lead to changes in cell membrane potential, creation of reactive oxygen species (ROS) and changes in synaptic and glutamate transporter activity, resulting in a drop in the seizure threshold. These changes could also explain comorbidities, such as anxiety and cognitive deficits (Han et al., 2021). This highlights the need for treatment strategies to improve brain energy metabolism and supply of alternative energy carriers.

In neurons and glial cells, an increase in KBs has been associated with an increase in mitochondria and ATP production, therefore maintaining the resting membrane potential, reducing the amount of ROS production and changing neurotransmitter levels (Yudkoff et al., 2001; Melø et al., 2006; Nylen et al., 2009; Milder et al., 2010). Neurotransmitter changes seen with a KD are a decrease in the excitatory neurotransmitter glutamate and an increase in the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and neuropeptide Y (an endogenous anticonvulsant), supporting its anti-seizure effect (Lin et al., 2000; Wang et al., 2003; Melø et al., 2006). Specifically, the KBs beta-hydroxybutyrate and acetoacetate compete with chloride ions at the site of allosteric regulation of the vesicular glutamate transporter and thus inhibit glutamate release, resulting in decreased presynaptic glutamate release (Juge et al., 2010). On the other hand, the metabolism of KBs leads to increased production of oxaloacetate. The latter is diverted into the tricarboxylic acid (TCA) cycle to provide cellular energy. This reduces the amount of oxaloacetate available for conversion of glutamate to aspartate, thereby increasing the conversion of glutamate to GABA (Yudkoff et al., 2008). In addition, the MCFA decanoic acid can also directly inhibit glutamatergic AMPA receptors and the mTORC1 (mechanistic target of rapamycin complex 1) signaling pathway (Chang et al., 2016; Warren et al., 2020).

The anti-seizure effect of a KD and MCT might also work through the MGBA. A study in two mouse models showed that the GIM is both necessary and sufficient to increase seizure threshold as a response to the KD. Seizure protection could be restored by transplanting GIM from KD treated mice to mice depleted with antibiotics and by postnatal conventionalizing as well as treatment with specific KD mediated GIM, i.e. *Akkermansia* and *Parabacteroides,* in germ-free mice. The seizure protection in mice receiving a KD was GIM mediated via changes in the GABA/glutamate ratios in the hippocampus (Olson et al., 2018). In a canine study, *Bacteroidaceae* species within genus 5–7N15 were more

[2] See: FEDIAF Scientific Advisory Board. Carbohydrates in dog and cat food. https://europeanpetfood.org/wpcontent/uploads/2022/02/FS_Carbohydrates.pdf (Accessed 24 October, 2022).

Table 1
Microbiota identified as associated with epilepsy and/or its treatment [a].

Reference	Dietary intervention	Study type	Duration	Number of patients/ animals included	Level of evidence	Seizure frequency	Changing microbiome	
							Decrease	Increase
Xie et al., 2017	Classic KD	Prospective dietary trial	1 week	14 infants with DRE	IV	64 % of infants showed improvement, 50 % SF reduction	- *Proteobacteria* - *Cronobacter*	- *Bacteroides* - *Prevotella* - *Bifidobacterium*
Olson et al., 2018	KD 6:1	Prospective experimental study	2 weeks	5–21 mice at each time point	I	Increase in seizure threshold	- alpha diversity	- *Akkermansia muciniphila* - *Parabacteroides* - *Sutterella* - *Erysipelotrichaceae*
Zhang et al., 2018	Classic KD	Prospective dietary trial	6 months	20 Children with DRE	IV	50 % showed > 50 % SF reduction	- Firmicutes	- Bacteroidetes
Lindefeldt et al., 2019	Classic KD	Prospective dietary trial	3 months	12 Children with DRE	II	> 50 % SF reduction	- Bifidobacteria - *E. rectale* - *Dialister*	- *E. coli*
Pilla et al., 2020	10 % MCT-included complete diet	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	11 dogs (IE Tier II)	I	NA	- *Blautia* - *Megamonas*	- *Erysiopelptrichaceae* - *Fusobacteriaceae* - *Bacteroidaceae* Species from genus 5–7N15
Gong et al., 2021	Classic KD	Prospective dietary trial	6 months	12 children with DRE	II	66 % showed > 50 % SF reduction	- *Bifidobacterium* - *Akkermansia* - *Actinomyces* - *Enterococcaceae*	- *Subdoligranulum* - *Dialister* - *Alloprevotella*

DRE, drug-resistant epilepsy; KD, ketogenic diet; NA, not applicable; SF, seizure frequency.
[a] The table displays information about studies in animals and humans with epilepsy associated with gastro-intestinal microbiome changes after dietary interventions with a ketogenic diet and medium-chain triglycerides. The diagnostic classification derives from the International Veterinary Epilepsy Task Force (De Risio et al., 2015).

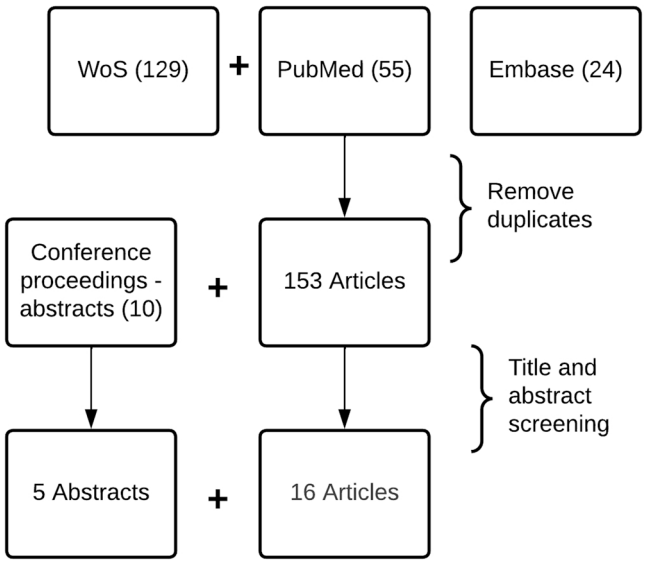

Fig. 1. Flowchart illustrating the comprehensive search strategy that was performed for this review. First online databases were searched using the following search terms ((epileps* OR seizur*) AND (canin* OR dog*) AND (nutrition* OR diet*)) on the MEDLINE database via the PubMed interface, ALL= ((epileps* OR seizur*) AND (canin* OR dog*) AND (nutrition* OR diet*)) on Web of Science (WoS) and (epilepsy:ti,ab,kw OR seizure:ti,ab,kw) AND (canis:ti,ab,kw OR dog:ti,ab,kw) AND (nutrition:ti,ab,kw OR diet:ti,ab,kw) on Embase. All searches were performed on 02 July 2021. Thereafter, the authors received notification when new literature was identified matching these search terms. Duplicates were removed and a manual search through the conference proceedings of both European College of Veterinary Neurology (2005–2021) and European Society of Veterinary and Comparative Nutrition (2013–2021) were performed. In a final step, a title and abstract screening on relevance was performed, identifying a total of 21 publications that reported a nutritional intervention for a canine population diagnosed with idiopathic epilepsy.

abundant in dogs fed MCTD (Pilla et al., 2020). *Bacteroidaceae*, including genus 5–7N15, have previously been associated with the reduction of aggressive behaviour in dogs and fulfill a similar role as *Akkermansia* in humans. However, changes in GIM composition seen in animal and human patients with epilepsy fed KD and MCTD are different (Table 1). The causes of the differences between these studies could be multifactorial involving species difference, age of the targeted group, type and ratio of the diets and duration of the study. Other than changes in microbial diversity, the alteration of their functions is important to consider, which is lacking in most studies. The KD modulates a functional change in the GIM that increases the SCFA production (Lindefeldt et al., 2019; Gong et al., 2021). Many bacteria of the canine core GIM can produce SCFA from plant polysaccharide fermentation, which can circulate to the brain (Oldendorf, 1973; Pilla and Suchodolski, 2021). Particularly butyrate, one of the SCFA, induces an anti-inflammatory effect through multiple pathways including downregulation of proinflammatory mediators (Chang et al., 2014), which could contribute to the satisfactory outcome of seizure control (Watanangura et al., 2022). Furthermore, serum metabolites of phospholipids, i.e. phosphatidylcholine and acylcarnitine, were altered in dogs with IE on MCTD by an increase in C17:0 moieties, potentially resulting in an increase in the production of the anti-seizure triglyceride triheptanoin (Law et al., 2018).

Two preliminary studies investigated the role of a classic KD in dogs with drug-resistant epilepsy. One study reported a decrease in seizure frequency (SF) compared to baseline in both the KD and control diet, but no significant difference between both groups (Patterson et al., 2005). The second KD study reported a decrease in SF compared to baseline, but no control group was implemented (Pagani et al., 2014). However, both studies were underpowered, as noted by the authors. One of the side effects of a classic KD is pancreatitis (Martin-McGill et al., 2020), which is not reported in MCTD.

A total of eight studies have been published on the use of MCTs in dogs with IE, four of which specifically investigated the effect of MCTD (MCT: 9–12 % of metabolisable energy) on the SF in dogs with IE. All dogs were receiving ASDs, but no changes to the medical treatment were made during the dietary trial. More details on the diet composition are depicted in Table 2. Seizure freedom was achieved in 7–14 % of dogs, 11–43 % of dogs had at least 50 % reduction, 24–43 % of dogs had less than 50 % reduction and in 14–39 % of the cases no reduction in SF was observed (Berk et al., 2020; Law et al., 2015; Molina et al., 2020). In contrast to supplementing MCTs to any basal diet, a complete diet including MCTs seems to have a better response. Approximately half of the dogs showed a decrease in SF of at least 50 % in a complete MCTD (Law et al., 2015; Molina et al., 2020), in contrast to only 18 % of the dogs with a reduction of at least 50 % when adding MCTs as supplement (Berk et al., 2020). Nutrient interaction might play a role in these differences. For example, the protein content could interfere with MCT transportation to the liver via albumin (Brody, 1994) and high dietary fat requires increased antioxidants (Harris and Embree, 1963). The wide range of basal diets, i.e. dry food, home cooked food, raw food and combinations of these with or without wet food included in the trial with MCT-supplement makes it impossible to draw conclusions about nutrient interactions in this population (Berk et al., 2020). The use of MCT-supplements can be, however, a valuable alternative for dogs who have additional dietary requirements for other diseases like obesity, kidney disease or urolithiasis.

Elimination diets and gluten-free diets

An adverse reaction to food (ARF) is described as the immunological (food allergy) or non-immunological (food intolerance) reaction of an individual to an otherwise harmless dietary component (Cianferoni and Spergel, 2009). Diagnosis and treatment for ARF in dogs consists of a strict elimination diet and dietary challenge, i.e. a diet that does not contain allergens for that individual, followed by original diet provocation (Gaschen and Merchant, 2011). Therefore, a novel or hydrolysed protein source is used (Roudebush et al., 2010). Mostly gastro-intestinal or dermatological clinical signs are linked to ARF, but in the literature, an association is described with other organs including the CNS in dogs (Gaschen and Merchant, 2011). However, there are no original studies supporting this statement. One specific type of elimination diet, the gluten-free diet, has received more attention as a management option for neurological diseases (Durazzo et al., 2022).

There is currently a large gap between scientific evidence regarding the role of gluten in dogs with IE and the anecdotal information available on the internet. For paroxysmal dyskinesia in Border Terriers and Maltese dogs, however, studies suggest that a gluten-free diet can reduce the frequency and/or severity (Lowrie et al., 2018; Polidoro et al., 2020). Both types of paroxysmal episodes can be hard to distinguish. Therefore, this could lead to misdiagnosing IE and consequently contribute to the belief that gluten reduces epileptic seizures. There is only one preliminary retrospective study that included IE in the investigation of serological markers for gluten sensitivity in dogs with different types of paroxysmal disorders. Anti-gliadin antibodies (AGA) and anti-transglutaminase-2 antibodies (ATG2) were measured in the serum of dogs with IE ($n = 11$), Lafora disease ($n = 5$), paroxysmal dyskinesia ($n = 14$) and tremors ($n = 2$). A significantly higher ATG2 concentration was found in dogs with IE compared to Lafora disease and paroxysmal dyskinesia. The severity of the clinical signs was not associated with the concentration of AGA or ATG2. No differences were found for AGA in any of the groups (Gödel et al., 2021). However, the study has a low level of evidence (IV) and it lacks any evidence of causality: the presence of serum antibodies only confirms exposure to a food antigen and not a food allergen.

It is hypothesised that the peripheral inflammatory processes

Table 2
All canine clinical studies including nutritional interventions for the management of idiopathic epilepsy.

Reference	Dietary intervention	Study type	Duration	Number of dogs included	Level of evidence[a]	Seizure frequency
Patterson et al., 2005	KD: 57 % fat, 28 % protein and 5.8 % NFE	Prospective, randomised double-masked, placebo-controlled dietary trial	6 months	17	II	SF at 0–6 m on KD = 2.02–2.41/month - SF at 0–6 m on placebo = 2.35–1.36/month – 2/6 dogs SF decrease > 50 % in both placebo and KD
Pagani et al., 2014	KD: 65 % fat, 25 % protein and 7 % CH	Prospective dietary trial	2 months	5	IV	SF decrease compared to baseline - no numerical data available
Law et al., 2015[d]	10 % MCT-included complete diet[c]	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	21	I	SF on MCT = 2.31, 0–9.89/month - SF on Placebo = 2.67, 0.33–13.82/month[b] - 10/21 dogs SF decrease > 50 % on MCT
Packer et al., 2016	10 % MCT-included complete diet[c]	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	21	I	SF on MCT = 2.31, 1.00–4.46/month - SF on Placebo = 2.67, 1.78–4.91/month[b]
Law et al., 2018[d]	10 % MCT-included complete diet[c]	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	21	I	NA
Berk et al., 2020[e]	9 % MCT-supplement on variable diets[c]	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	28	I	SF on MCT = 2.51, 0–6.67/month - SF on Placebo = 2.67, 0–10.45/month[b] - 5/28 dogs SF decrease > 50 % on MCT
Molina et al., 2020	12 % MCT-included complete diet[c]	Prospective multicentre dietary trial	84 days	21	II	SF on MCT = 1.7 (± 0.4) - SF at baseline = 2.5 (± 0.3)[b] - 9/21 dogs SF decrease > 50% on MCT
Pilla et al., 2020[d]	10 % MCT-included complete diet[c]	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	11	I	NA - primary outcome = faecal microbiome and lipidomic profile
Berk et al., 2021[e]	9 % MCT-supplement on variable diets[c]	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	18	I	NA - primary outcome = cognitive abilities
Berk et al., 2021a	9 % MCT-supplement on variable diets[c]	Double-masked, randomised, placebo-controlled crossover dietary trial	6 months	28	I	NA - primary outcome = metabolic alterations
Lujan et al., 2005	Elimination diet: One CH and one pr source	Case-series	NA	8	IV	Six dogs seizure-free, One dog reduced SF
Gödel et al., 2021	No intervention	Prospective diagnostic study	NA	32	IV	NA - primary outcome = association of serological markers
Scorza et al., 2009	oral fish oil supplementation 2 g/day	Case report	18 months	1	V	SF at baseline 3/ month - SF on supplement 0.33/ month
Matthews et al., 2012	Supplement 400 mg EPA, 250 mg DHA and 22 mg vit E per 10 kg BW	Masked placebo-controlled cross-over trial	24 weeks	15	I	Number of seizures: supplement = 2.85 (0–18) - placebo = 4.38 (0–24) BUT paired *t*-test not significant
Mogi et al., 2018	Hemp oil 0.51–5.0 mg CBD/kg day PO	Case series	8 weeks	3	IV	Two owners reported improvement - one owner reported no changes
McGrath et al., 2019	CBD-infused oil 2.5 mg/kg BID PO	Double-masked placebo-controlled clinical trial	12 weeks	26	II	CBD: 2/9 decrease in SF > 50 % - placebo: 2/7 decrease in SF > 50 %
Trepanier and Babish, 1995	Dry petfood with chloride contents of 0.2 %, 0.4 % and 1.3 % on DM	Randomised prospective comparative study	8 weeks	12	II	NA - study in healthy dogs
Shaw et al., 1996	Canine s/d diet, Hills Pet Nutrition	Case report	NA	1	V	21 months seizure freedom after dietary adaptation
Maguire et al., 2000	Maintenance diet: 4.8 g pr and 4.6 g fat/100 kcal – pr restricted diet: 3.4 g pr and 4.6 g fat/100 kcal – fat and pr restricted diet: 5.2 g pr and 2.7 g fat/100 kcal	Randomised prospective comparative study	2 months	27	II	NA - study in healthy dogs
Togawa et al., 2018	No intervention	Prospective observational study	NA	23	II	NA - primary outcome = relation dietary Cl and serum Br
Fantinati et al., 2021	Dry hydrolysed diet and over-the-counter adult dry diet	Case report	NA	1	V	NA - bromide toxicosis

Br, bromide; BW, body weight; CBD, cannabidiol; CH, carbohydrates; Cl, chloride; DHA, docosahexaenoic acid; DM, dry matter; EPA, eicosapentaenoic acid; KD, ketogenic diet; MCT, Medium chain triglycerides; NA, not applicable; NFE, nitrogen-free extract; PO, per os; pr, protein; SF, seizure frequency.
a All studies were identified using the search strategy illustrated in Fig.1. This process revealed 21 relevant publications. These were graded based on the Elsevier level of evidence hierarchy for treatment studies[11], as described in the table with grades I-V. In this hierarchy, studies assigned to level I have the highest level of evidence.
b $P < 0.05$.
[a] Based on metabolisable energy.
[b, c] Data presented from the study population with the same letter.

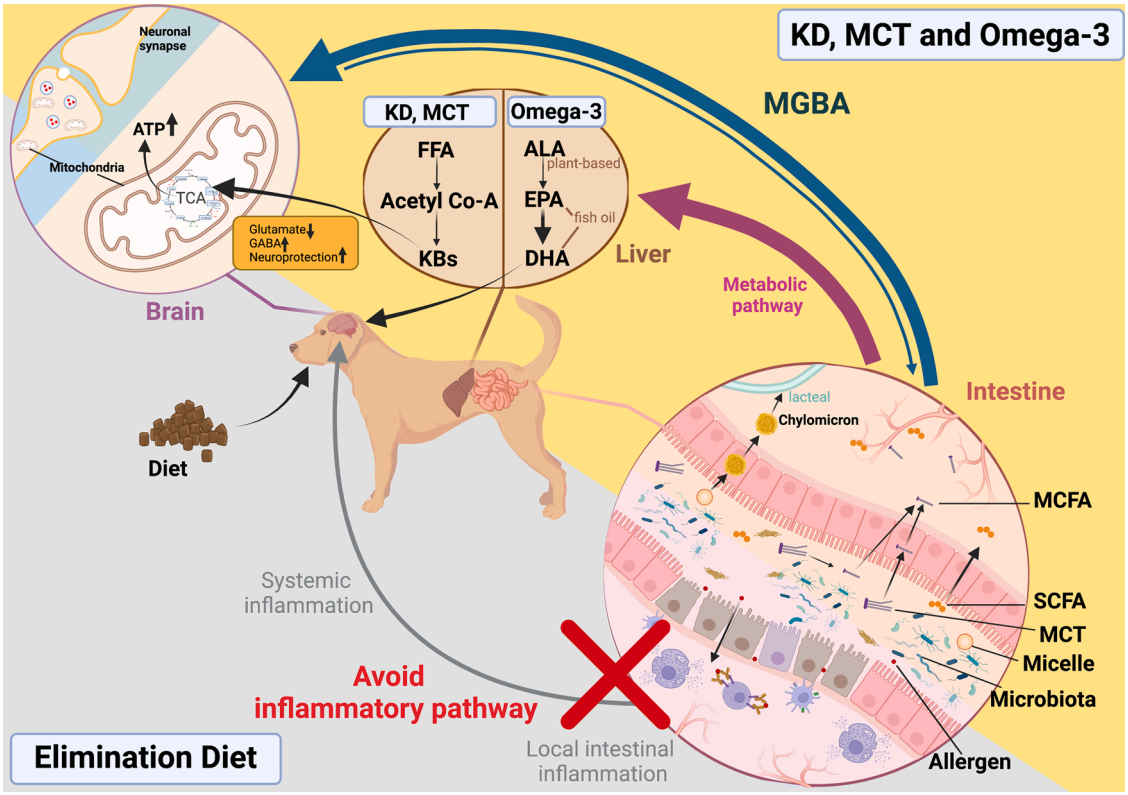

Fig. 2. Diagram demonstrating the pathways for the ketogenic diet (KD), medium chain triglycerides (MCT), omega-3 fatty acids (FAs) and elimination diet. In the KD, the fatty acids (FA) have to be digested in the intestines before passing through the systemic circulation. The absorption of FA differs between the different sizes. Medium chain fatty acids (MCFA) derived from MCT and short chain fatty acids (SCFA) can enter the circulation rapidly and proceed to the liver, while long chain fatty acids (LCFA) including omega-3 FAs form chylomicrons and enter the lacteal circulation before being transported to the liver. Free fatty acids (FFA) are converted to Acetyl Co-A by beta-oxidation and change to ketone bodies (KBs) primarily in the liver before entering the brain. Regarding omega-3 FAs, docosahexaenoic acid (DHA) is most important for the brain. Only a small percentage of linolenic acid (ALA) is converted to DHA in the liver, the majority thereof is food-derived. In the microbiota-gut-brain axis (MGBA), gastro-intestinal microbiota is affected by nutrition which can change both its diversity and functional products. In addition, the mechanism of action for elimination diets is different from lipid-sourced diets. The purpose of an elimination diet is to avoid inflammation following antigen activation. (Created by [31]).

following an ARF relate to the pathophysiology of IE (Frediani et al., 2001; Frediani et al., 2004; Gorjipour et al., 2019) and may work through immune system signaling pathways via the MGBA (Falsaperla et al., 2017). This process starts with activation of antigen-presenting cells leading to secretion of proinflammatory cytokines from T-helper-2 and mast cells in the intestine, resulting in an increase in intestinal permeability (Falsaperla et al., 2017; Gorjipour et al., 2019). The increase in intestinal permeability leads to invasion of cytokines, toxic metabolites, bacteria and small molecules from the intestinal lumen to the blood circulation, causing systemic inflammation (Fig. 2). These active cytokines increase the permeability of the BBB, resulting in temporary or long-term seizure susceptibility due to BBB disturbance or a 'leaky brain' (Riazi et al., 2010). This could be aggravated by peptidoglycan from the cell wall of leaked bacteria, that enters the brain and causes chronic inflammation (Laman et al., 2020). Moreover, the neuronal excitability could also be altered as a result of microglial stimulation and from an increase in proinflammatory cytokines in the brain, promoting epileptic seizures (Riazi et al., 2008). The aim of an elimination diet is to eliminate the possibilities of the previously mentioned processes. There is growing evidence for the role of inflammation in epileptogenesis. However, the role of the GIM in this type of diet is probably negligible (Martinez-Lopez et al., 2021).

In children, food allergies were linked with epilepsy in a Scandinavian case-control study and a US-population based study (Frediani et al., 2001; Silverberg et al., 2014). There is one retrospective case-series ($n = 8$) investigating the management of IE with an elimination diet in dogs. Seizure frequency decreased in 7/8 dogs, whereas it ceased completely in six dogs while on the elimination diet. One dog did not show improvement in SF. Only four dogs were challenged with different food and the seizure activity recurred, which confirms an ARF (Luján et al., 2005). More recently, a 12-week dietary trial in 32 children with food allergies and drug-resistant epilepsy was performed: 50 % showed seizure freedom and another 35 % showed at least a 50 % decrease in SF when on the elimination diet; however, no challenge was included (Gorjipour et al., 2019).

In conclusion, only two level IV studies are available, indicating that more studies are needed to support the elimination diet as an evidence-based part of the management of canine IE. Furthermore, the relation of gluten-sensitivity and IE is still questionable.

Nutraceuticals

The term 'nutraceuticals' was defined in 1989 as 'food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease' (Brower, 1998). Clinical evidence of nutraceuticals in canine IE is still scarce; however, almost half of 297 owners indicated using dietary supplements for their dogs after epilepsy diagnosis (Berk et al., 2018). The top five rankings were coconut or coconut-derived oils (77.3 %), fish or fish-derived oils (66.9 %), milk thistle (42.7 %), cannabis oil (42 %) and thiamine products (24.8 %;

[1] See: Levels of evidence. https://www.elsevier.com/_data/promis_misc/YJPSU-Levels-of-Evidence.pdf (Accessed 24 October 2022).

Berk et al., 2018). Nonetheless, only coconut or coconut-derived oil (containing MCTs), fish or fish-derived oils (containing omega-3 fatty acids) and cannabidiol (CBD; one of the cannabinoids that can be found in cannabis oil) have been scientifically investigated.

Omega-3 fatty acids

Omega-3 fatty acids are essential long-chain polyunsaturated fatty acids (PUFAs) with a double-bond at the third carbon, which are known to play an important role in the maintenance of health in animals and humans (Bauer et al., 2011; Calder, 2012). The three major omega-3 fatty acids are linolenic acid (ALA), found in walnuts, flaxseed, soybean and canola oil, and its derivatives eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) typically found in fish and fish-derived oils (Bauer, 2007).

The CNS contains the second highest amount of lipids, preceded only by adipose tissue. Lipids constitute 60 % of brain dry mass, and half of these are PUFAs (Taha et al., 2010). Omega-3 PUFAs are transported from the intestines to the liver before entering the brain (Rapoport et al., 2007; Fig. 2). However, the conversion in the liver from ALA to DHA is limited to less than 10 % in mammals (Bauer, 2007; Brenna et al., 2009). Docosahexaenoic acid is the most important omega-3 PUFA for the brain, as a structural component of neuronal membranes, by affecting cell signalling and modulating the synthesis of phosphatidylserine (Dyall, 2015). Therefore, plant-based sources of omega-3 fatty acids containing ALA are considered less effective for neurological support than fish-oil containing EPA and DHA. Omega-3 PUFAs, particularly DHA, are anti-excitatory, anti-inflammatory and have neuroprotective effects. The anti-excitatory effect is explained by inhibition of voltage-gated sodium and calcium channels on the cell membrane, resulting in an increase in seizure threshold (Nathan et al., 2019). Moreover, seizure threshold can also be elevated by DHA by activating some types of peroxisome proliferator-activated receptors (PPARs), a potential ASD target (Saha et al., 2014; Gavzan et al., 2018). DHA and EPA are both important in inhibiting the cyclooxygenase-2 synthesis and decreasing proinflammatory prostaglandin E2 (Rees et al., 2006; Roman et al., 2006; Lee et al., 2009). Lastly, DHA and EPA can increase mitochondrial uncoupling protein expression, resulting in a reduction in ROS generation (Sullivan et al., 2004; Davis et al., 2008).

Only two publications investigated the use of omega-3 fatty acids in dogs with IE (Scorza et al., 2009; Matthews et al., 2012). A reduction in SF was first described in a case report about a two-year-old female Great Dane diagnosed with IE on an appropriate dose of phenobarbital (Pb). Seizure frequency decreased from three per month to one every three months by supplementing 2 g fish oil per day. The amount of omega-3 FA per metabolic weight associated with this supplement was not described (Scorza et al., 2009). However, a masked-placebo controlled cross-over trial ($n = 15$, two periods of 12 weeks) could not confirm this positive result with a supplement containing 400 mg EPA, 250 mg DHA and 22 mg vitamin E per 10 kg of bodyweight (BW; Matthews et al., 2012). This dosage is similar to what is established for atopy and inflammatory bowel disease in dogs (700 mg EPA+DHA/10 kg BW; Bauer et al., 2011). In a human placebo-controlled clinical trial, a significant reduction in SF was only described with a low-dose fish-oil in contrast to a high-dose fish-oil supplement, indicating that adequate doses are indeed crucial (DeGiorgio et al., 2015). Rat models suggest that a minimal duration of three months is needed to increase seizure threshold (Taha et al., 2013), indicating that treatment duration might have been too short in the canine study (Matthews et al., 2012) and that the carry-over effect between the supplementation and placebo phase may have occurred, since no wash-out period was included and PUFA supplementation was always used first. Possible side effects of omega-3 FA are reported, but a safe upper limit of 2080 mg EPA+DHA/10 kg BW (Lenox and Bauer, 2013) is recommended by the National Research Council. Additional health benefits like a reduction in blood pressure, reduction in the risk of sudden unexpected death in human patients with epilepsy (Scorza et al., 2013; DeGiorgio and Taha, 2016) and a synergistic interaction with ASDs, possibly lowering the dose of medication (carbamazepine, valproate and levetiracetam) have been described (Pages et al., 2012; Abdel-Dayem et al., 2014; Abdel-Wahab et al., 2015). Overall, the level of evidence for the use of omega-3 FAs in canine IE is still low, only one level I study having been performed in which no significant effects were shown. Future research should therefore focus on larger placebo-controlled trials of longer duration, well-defined baseline SF characteristics, complete diets with an increased EPA+DHA content and the establishment of doses for dogs with IE, considering ASD interactions.

Cannabidiol or cannabis oil (CBD)

Cannabidiol is a non-psychoactive cannabinoid from the *Cannabis sativa* plant (Martinez et al., 2020). It can be used both as an oral supplement or intranasally. Due to practical aspects, the oral route is most favorable. However, the intranasal route provides more rapid absorption and can be an alternative method (Polidoro et al., 2022).

Anti-seizure activities of CBD seem to work through multi-mechanisms, such as antagonism of G protein-couple receptor 55 (GPR 55), agonism of transient receptor potential vanilloid type 1 (TRPV1) and adenosine reuptake, while having low affinity at endocannabinoid receptors (Ibeas Bih et al., 2015; Johannessen Landmark et al., 2021). More details are discussed in the review article by Potschka and colleagues in this special issue (Potschka et al., 2022).

There are only two clinical studies in dogs with refractory IE (Tier II confidence level) under ASD treatment using CBD from hemp. In one study, dogs were randomised to receive CBD ($n = 12$) or placebo ($n = 14$) at 2.5 mg/kg every 12 h for 12 weeks. Almost 40 % of the dogs were excluded during the study due to ASD adjustment, discontinued appointments, progressive adverse effects and euthanasia. A significant SF reduction of around one-third compared to pre-treatment SF was found in the CBD-group. However, the proportion of responders between the groups showed no difference, when at least 50 % decrease in seizure activity was defined as a responder. Adverse effects were only observed in the CBD group, resulting in the exclusion of three dogs from the trial. From these, two developed proprioceptive ataxia, while one dog had severe status epilepticus. However, the latter was most likely the consequence of the dog's seizure condition rather than an adverse effect of CBD. Serum alkaline phosphatase activity was significantly increased in the CBD group due to suspected cytochrome P450 isoenzymes induction in the liver, so that monitoring of liver function is recommended, especially in dogs treated with Pb (McGrath et al., 2019). The second study was a 24-week randomised crossover trial in fourteen dogs comparing CBD and cannabidiolic acid (CBDA)-rich hemp extract at 2 mg/kg orally every 12 h. The results revealed a statistically lower SF during the CBD/CBDA-rich hemp treatment phase with six dogs experiencing at least 50 % reduction in SF compared to the placebo phase and no dogs showing at least 50 % reduction in SF. Adverse events observed during treatment were somnolence and ataxia in three and four dogs, respectively (Garcia et al., 2022). A small scale case series supported a decrease in SF with CBD in three dogs with IE Tier I (Mogi and Fukuyama, 2019). Due to small sample sizes in both those studies (one level IV and one level II study; Table 2), the effect of CBD in dogs with IE remains questionable. More studies are needed to provide more details about the anti-seizure effect, optimal dose and drug interactions with ASDs in dogs with IE. In addition, no significant drug-interaction between variable dosage of CBD and Pb in healthy dogs was detected (Doran et al., 2021). Based on current regulations in the European Union (EU), CBD is hard to categorise because it is neither a narcotic, drug (ECLI:EU:C:2020:938) nor food (Regulation (EU) 2015/2283), making product instruction, labelling and concentration control difficult.

[3] See: BioRender. https://biorender.com (Accessed 25 October 2022).

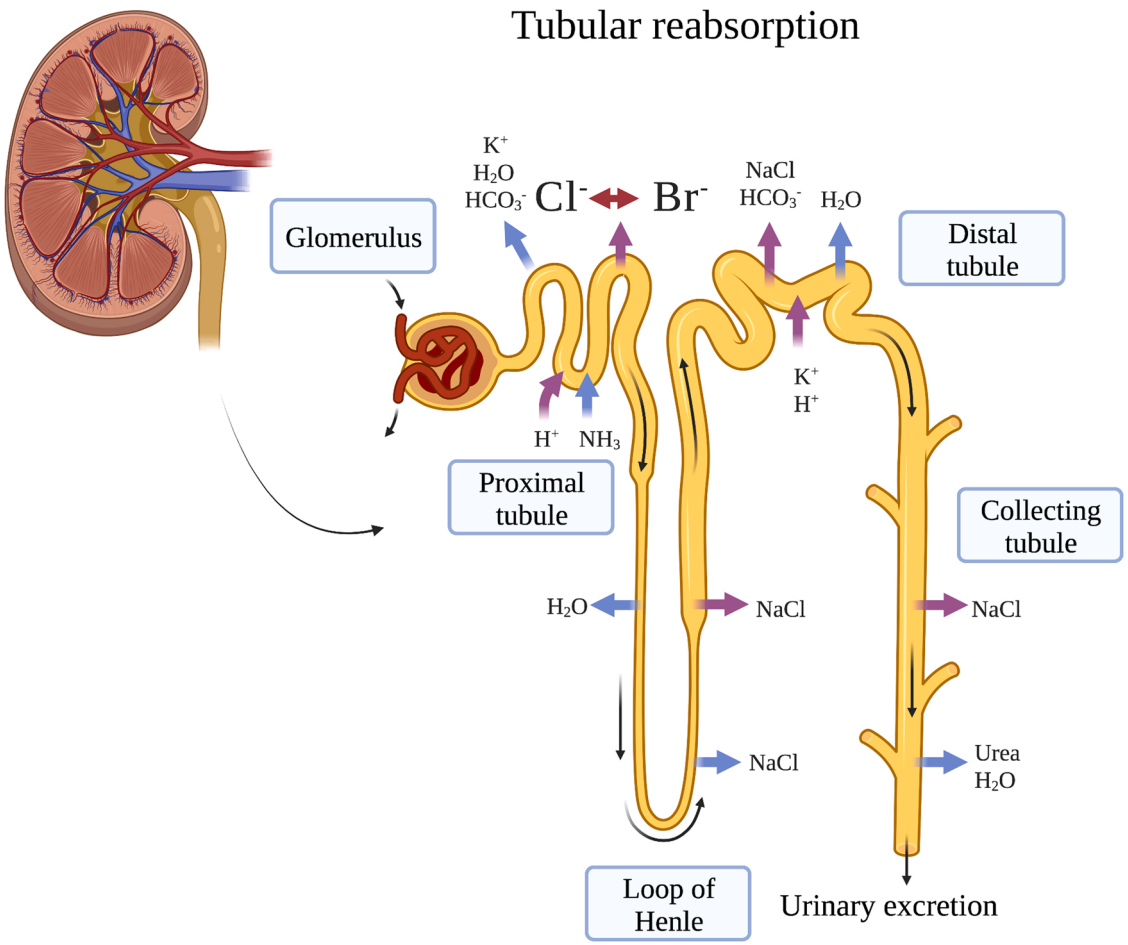

Fig. 3. Illustration showing the tubular reabsorption of different ions, including chloride and bromide. Chloride and bromide ions are reabsorbed in the proximal tubule which causes a competition between both ions. The reabsorption of bromide is stronger, compared to chloride, if both ions are present in similar concentrations. When more chloride is available from the diet, fewer bromide ions are reabsorbed, and therefore more bromide ions are excreted in the urine. This causes a decrease in the biological half-life of bromide. (Created by [3]).

Table 3
The impact of chloride content on potassium bromide serum concentration, a summary of two case reports.

	Signalment	SC KBr at start	DC	SC KBr after DC	Adaptation	SC KBr after adaptation
Shaw et al., 1996	11-year-old Dachshund	1100 mg/L	41 % Cl increase	410 mg/L	Change to previous diet	990 mg/L
Fantinati et al., 2016	3-year-old Tibetan Mastiff	1380 mg/L	53 % Cl decrease	2800 mg/L	Decrease dose KBr 15 %	1500 mg/L

Cl, chloride content, DC, dietary change; SC, serum concentration.

Furthermore, the enforcement is different in each EU member state. Therefore, selecting CBD products regarding their concentration and dose can vary significantly.

Effects of diet on anti-seizure medication

The effect of chloride content on bromide serum concentration has been known since 1995. The competition between those two ions for tubular reabsorption explains the changes in its clearance (Fig. 3). In general, the pharmacodynamic and pharmacokinetic properties of bromide can be explained by its competitive behaviour on chloride ion channels throughout the body and brain. This explains the higher clearance rate of bromide when higher concentrations of chloride are present in the food and vice versa. Similarly, serum biochemistry analysers record bromide as a chloride ion, resulting in laboratory tests being returned as 'pseudohyperchloraemia'. Feeding trials in healthy Beagles receiving a diet with 1.3 %, 0.4 % or 0.2 % chloride of a dry matter content showed that a higher chloride concentration decreased the biological half-life of bromide significantly and the required doses subsequently had to be increased to maintain optimal serum concentrations (Trepanier and Babish, 1995).

In 2018, a formula to describe this relationship was established using the dietary chloride content and serum bromide concentration from 23 client-owned dogs. A strong negative correlation was found: $y = -0.2x + 87$ with y: serum bromide concentration per dose (µg/mL per mg/kg/day) and x: dietary chloride intake per body weight (mg/kg/day; Togawa et al., 2018). This formula provides a good guideline in clinical practice to optimise bromide dosages. However, chloride content is often not mentioned on product labels because it is not legally mandatory in the EU Regulation (EC) 767/2009, which complicates the practical use of the above mentioned formula.

The clinical impact on the obtained bromide serum concentrations is illustrated in two case reports (Table 3). The first dog had a cluster of five seizures two weeks after dietary transition from a struvite-preventive diet to a calculolytic diet. Therefore, the dog returned to the previous diet with a lower chloride content and received a loading

dose of potassium bromide (KBr) over several days, which restored seizure control (Shaw et al., 1996). The second dog developed progressive signs of bromism two months after a dietary switch from a dry hydrolysed diet to an over-the-counter adult dry diet. Signs resolved within four months by reducing the KBr dosage while strictly avoiding any further dietary changes (Fantinati et al., 2021).

Besides the interaction with bromide that is well established, there are some data to support an interaction between the diet and Pb concentrations, too. Healthy Beagles ($n = 27$) fed a protein-restricted or protein- and fat-restricted diet had a significantly lower biological half-life of Pb and a significantly higher increase in serum alkaline phosphatase activity than on a maintenance diet. The nutritional composition of these diets is displayed in Table 2. Furthermore, dogs fed a fat- and protein-restricted diet had a significantly higher clearance rate for Pb (Maguire et al., 2000). These effects are assumed to be the result of alteration in the hepatic metabolism (Fettman and Phillips, 2000). Furthermore, the elimination of Pb could be influenced by an urolithic type of diet, as it was shown that the urinary excretion of a single-dose Pb (3 mg/kg) could be decreased or increased by urinary acidification with ammonium chloride or alkalinisation with potassium citrate, respectively (Fukunaga et al., 2008).

This stresses the importance of re-evaluating drug dosages with every dietary change both for dogs on KBr, supported by two level II clinical studies and two case reports (level V) evaluating the interaction with chloride, and Pb, supported by one level II study evaluating the interaction with protein and fat content of the diet.

Conclusion

It is a fact that nutrition should be considered in the management of dogs with IE alongside ASDs. However, only MCT-enriched diets can be supported with a satisfactory level of scientific evidence in veterinary medicine, whereas scientific evidence for the majority of the nutritional interventions discussed remains limited, thus leaving important opportunities for future research. Nutrition could not only influence epileptic seizure control positively, but also has an impact on the pharmacokinetic properties of ASDs. In clinical practice, an optimal diet should be tailored to the individual patient, ideally in consultation with a nutritionist, considering other metabolic and gastrointestinal diseases apart from epilepsy, epilepsy comorbidities and medical treatments such as ASDs.

Conflict of interest

FV is currently working on a doctoral research project regarding the role of the GIM and nutrition in canine IE, which is financially supported by Nestle Purina. JS and MH are Members of the Advisory Board of Nestle Purina Petcare. JS receives consulting fees from Royal Canin and Hill's Pet Nutrition, Inc. HV served as paid consultant in the field of epilepsy for Boehringer Ingelheim, CEVA Animal Health, Nestle Purina and as contract researcher for Boehringer Ingelheim, Desitin Pharma and Nestle Purina. MH has been paid for several consulting services by a variety of pet food companies. 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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