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Review

The gut microbiome and epilepsy

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ABSTRACT

Recently, evidence from both animal studies and human cases has emerged that a dysbiosis in the gut may be associated with certain forms of epilepsy. The ketogenic diet is an alternative treatment of drug-resistant epilepsy, although its precise mechanism of action has been unclear. It has now been shown that the ketogenic diet changes the composition and function of the gut microbiome in epilepsy patients. Studies in mice have demonstrated that the gut microbiota was necessary for the therapeutic effect of the diet and a mechanism of action has been proposed, providing new potential strategies for treatment. Further studies are needed to confirm the clinical relevance of this discovery.

Below, we will discuss the scientific evidence of the role of the microbiome in seizure disorders, the impact of the ketogenic diet on the intestinal microbiota as well as the interactions described between commonly used antiepileptic drugs and intestinal microbial communities. We also discuss the potential of modulators of the gut microbiota as possible future anti-seizure therapeutics.

Contents

1. What is epilepsy?

Epilepsy is a disease of the brain defined by the propensity for an individual to have recurrent unprovoked epileptic seizures [1]. Seizures involve abnormal paroxysmal changes in the electrical activity of neurons and are linked to an imbalance of excitatory and inhibitory brain networks [2]. Glial cells also play a role in seizure generation as they modulate neural function by restoring homeostasis of ions as well as neurotransmitters glutamate and gamma-aminobutyric acid (GABA) [3]. Many underlying causes of brain dysfunction can lead to epilepsy among which cerebral malformations, CNS infection, trauma, stroke and genetic mutations in epilepsy genes are common. In many patients the cause of epilepsy remains unidentified. However, this depends to a large extent on the available resources for evaluation [4]. Epilepsy is associated with cognitive and behavioural impairments such as intellectual disability, cerebral palsy, autism spectrum disorder and ADHD. When a decision for treatment is made an antiepileptic drug (AED) is started in monotherapy. If adequate trials of two tolerated, appropriately chosen and used AEDs fail, the patient is considered to have drug-resistant epilepsy, which applies to 25–30% of the epilepsy

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population. Then other AEDs, brain surgery, vagus nerve stimulation and ketogenic diet are current treatment options.

2. The ketogenic diet as an alternative treatment of epilepsy

The ketogenic diet (KD) is a well-established, non-pharmacologic treatment used for many years in children with medically refractory epilepsy [5]. It is a high-fat, sufficient-protein and very low-carbohydrate diet. The diet is calculated with a ratio between 2:1 and 4:1 of fat to protein and carbohydrates combined. The ratio 4:1 contains four times as many grams of fat for every gram of protein and carbohydrate together. Here, 70–90% of the energy intake will be derived from fat. A specialized dietician calculates the macronutrient composition of the diet as a basis for each meal for the individual child. Vitamins and minerals are added. The treatment is initiated at an epilepsy centre by a specialized KD team.

KD induces ketosis, i.e. a state of elevated blood levels of ketone bodies converted in the liver from the dietary fat. These ketones are used as an alternative energy substrate for ATP production in the cells of the body including the brain. This metabolic shift induces many biochemical, metabolic and hormonal changes that may in part contribute to decreased neuronal excitability and reduced number of seizures.

Two randomized controlled prospective studies evaluated the efficacy of KD in medically refractory epilepsy in children. The responder rate, i.e. patients with a decrease in the number of seizures by ≥50%, was 38% and 50% respectively for the two trials [6,7].

It is not known why some patients respond well to the diet while others do not.

The underlying mechanisms of action of KD are not fully elucidated but recent studies have proposed several potential mechanisms. These include enhanced GABA-mediated inhibition, direct inhibitory actions of polyunsaturated fatty acids on ion channels, elevated levels of ATP which is converted to the inhibitory mediator adenosine as well as increased mitochondrial biogenesis and reduced oxidative stress [8]. Recently, it has also been proposed that the intestinal microbiota may be involved in KDs mechanism of action which will be discussed further.

3. The microbiome, diet and neurological disorders

The intestinal microbiota plays a central role in human health. It stimulates the immune system and provides colonization resistance towards potential pathogens. It comprises ~150 times more genes than the human genome [9], which offers a multitude of enzymatic reactions. Health promoting metabolites such as vitamins and short-chain fatty acids (SCFAs) are produced that impact both gut and peripheral health via several gut-organ-axes. One of such axes, the microbiota-gut-brain axis has gained tremendous attention in the research community in the past years. The gut microbiota and the brain can communicate bidirectionally through the central and enteric nervous systems as well as endocrine, immune, and metabolic pathways [10]. It has been shown that the intestinal microbiota influences CNS physiology and neurochemistry impacting behaviour, cognition, mood, anxiety and depression [11]. Intestinal dysbiosis has been associated with a variety of neurological disorders, e.g. autism [12], multiple sclerosis [13], Parkinson's [14], and Alzheimer's [15]. Recently, changes in the gut microbiota have been linked to seizure susceptibility as discussed in this review.

The composition of the gut microbiota is influenced by environmental factors and to a lesser extent by host genetics [16]. Diet is a major factor shaping the composition of the intestinal microbial community [17,18] and the outcome of a dietary intervention is influenced by the composition of the gut microbiota at the time of intervention [19]. Research has focused in part on the impact of carbohydrates where certain types of dietary fibres known as microbiota-accessible carbohydrates (MACs) present an essential energy source to a healthy intestinal microbiota [20]. The ketogenic diet is extremely fibre-deprived and a few recent studies have investigated changes in the gut microbiota in patients with epilepsy during KD, which include diminished relative abundance of fibre-consuming bacteria such as bifidobacteria [21]. It is currently unknown whether changes in fibre intake or its effect on the gut microbiome contribute to the anti-seizure effect or whether this is only a potentially problematic consequence for the gut microbiome when increasing the dietary fat intake. More research is needed here.

4. Evidence for intestinal dysbiosis in epilepsy patients

There is some evidence that may suggest a potential role of the gut microbiota in epilepsy. In one case-report, a 22-year-old patient with Crohn's disease and a 17-year history of seizures received a faecal microbiota transplant (FMT) to treat Crohn's [22]. During the 20 months follow-up the patient was reported to be seizure-free despite discontinuing antiepileptic drug treatment with sodium valproate. Based on this case, a clinical trial for FMT for epilepsy patients has been registered (NCT02889627) but no results are yet available. In another study, probiotic treatment was shown to reduce seizure frequency by 50% or more in 28.9% of patients with drug-resistant epilepsy [23]. Braakman and Ingen also described six cases of drug-resistant epilepsy of which five became seizure free and one experienced an over 90% reduction in seizure frequency during a course of antibiotic treatment. This effect vanished within two weeks of cessation of the treatment, hypothetically due to a recovery of certain gut microorganisms [24] however other underlying mechanisms cannot be ruled out. Antibiotics may, for example, induce drug-drug interactions with AEDs that may attenuate or aggravate seizure propensity [25].

Furthermore, the gut microbiome of patients with drug-resistant epilepsy may differ from that of patients with drug-sensitive epilepsy [26]. In drug-resistant patients ($n = 42$), there was an increase in alpha diversity, i.e. within sample diversity, and relative abundance of rare bacteria mainly belonging to the phylum Firmicutes compared to drug-sensitive patients ($n = 49$). Bifidobacteria and Lactobacilli were associated with less than four seizures per year in both patient groups. 65 healthy controls were included in the analysis for alpha diversity. Unfortunately, taxonomic analysis was only performed comparing both patient groups. Thus, we do not know how much each patient group deviates from the healthy group, which is an intriguing question to answer.

To investigate whether epilepsy is associated with intestinal dysbiosis, larger cohorts and further clinical studies are needed. Intervention studies with pro- or antibiotics might explore new therapeutic strategies for epilepsy treatment, but we first need to determine which microbes are helpful or detrimental.

5. Dietary intervention studies in human cohorts

The ketogenic diet is an effective alternative treatment for drug-resistant epilepsy of various aetiologies. Its effect on the human gut microbiota has recently been studied [21,27–29] and will be discussed in the following paragraph. The major findings of these studies are also summarized in Table 1.

Glucose Transporter 1 Deficiency Syndrome (GLUT1 DS) is a genetic disorder often accompanied by frequent seizures. Here, a mutation in the gene of the glucose transporter protein type 1 (GLUT-1) severely impairs glucose uptake in the brain. Thus, KD is the treatment of choice in GLUT1 DS and it is often lifelong. Tagliabue et al. used RT-PCR to quantify changes of nine specifically targeted bacterial taxa in faecal samples of six Italian patients with GLUT1 DS three months after starting KD. They detected a significant increase in *Desulfovibrio* spp. during KD but no significant changes of any of the other taxa, i.e. Firmicutes, Bacteroidetes, *Bifidobacterium* spp., *Lactobacillus* spp., *Clostridium perfringens*, Enterobacteriaceae, *Clostridium* cluster XIV, and *Faecalibacterium prausnitzii*. *Desulfovibrio* spp. is a sulphate-reducing bacterium posing a potential detrimental effect on gut health, as sulphate-reducing bacteria have been associated with inflammatory

Table 1
Summary of studies investigating the effect of the ketogenic diet on intestinal microbiota in children with epilepsy.

Cohort	Number of Patients	Median Age (range)	Diagnosis	Time of Dietary Intervention	Specific Characteristics of KD	Analysis Method	Taxa of Lowest Assigned Level with Significant Decrease	Taxa of Lowest Assigned Level with Significant Increase	Major Functional Shifts	Publication
Italian	6	(8–34)	GLUT1 DS	3 months	Classic KD, majority of fat from animals (dairy products)	RT-PCR of 9 selected bacterial taxa	–	*Desulfovibrio* spp.	–	Tagliabue *et al.*
Chinese	14	1.95 (0.8–3.3)	Refractory epilepsy	1 week	Classic KD	16S rRNA gene sequencing	*Lachnoclostridium* *Hungatella* *Bifidobacterium* *Enterococcus* *Klebsiella*	–	–	Xie *et al.*
Chinese	20	4.2 (1.2–10.3)	Refractory epilepsy	6 months	Classic KD, 70% of fat from plants	16S rRNA gene sequencing	*Faecalibacterium* *Leucobacter* *Acinetobacter* *Pseudomonas* *Lachnospiracea insertae sedis* *Coprobacter* *Burkholderiaceae* *Ruminococcaceae*	*Bacteroides*	–	Zhang *et al.*
Swedish	12	7.7 (2.2–15.3)	Refractory epilepsy	3 months	Classic KD	Whole metagenomic shotgun sequencing	*Bifidobacterium longum* *Bifidobacterium adolescentis* *Eubacterium rectale* *Dialister*	*Escherichia coli*	Decrease in several pathways of carbohydrate metabolism Increase in hemin transport system	Lindefeldt *et al.*

GLUT1 DS, Glucose Transporter 1 Deficiency Syndrome.
KD, ketogenic diet.

bowel disease (IBD) [30,31]. The authors thus propose pre- or probiotics as possible supplementation during KD in patients with dysbiosis.

Two subsequent studies on the effect of KD on the gut microbiome were performed using 16S rRNA gene sequencing (region V3-V4) in Chinese children with drug-resistant epilepsy [28,29]. Xie et al. [28] analysed faecal samples from 14 infants with epilepsy and 30 age-matched healthy controls. The patients were sampled before and one week after KD. While there was no clear difference in alpha diversity, principal component analysis (PCA) revealed separation of the healthy controls from epilepsy patients, implicating a dysbiosis in these patients. One-week intervention with KD did not induce any global shifts. Relative abundances of individual genera were found to be significantly different between healthy controls and patients before starting KD, e.g. *Bacteroides, Cronobacter, Erysipelatoclostridium,* and *Bifidobacterium*. For many taxa these differences between healthy and diseased were reduced due to KD treatment. This reduction in patients during KD, however, was not statistically significant (false discovery rate above 0.37) and thus may indicate a shift to a healthier microbiome but with still substantial differences to a healthy gut community. Interestingly, *Cronobacter* was found to be the dominating genus in infants with epilepsy with a mean relative abundance of 23.3%, which decreased to 10.4% after one week on KD (p-value 0.04, FDR = 0.41). This genus was completely absent in the healthy group.

Zhang et al. [29] followed 20 patients with drug-resistant epilepsy for six months on KD. Alpha diversity did not significantly change with diet, but some clustering by treatment was observed in a principal coordinates analysis (PCoA). The authors detected a significant increase in the genus *Bacteriodes* upon treatment, and a decrease in a wide range of bacterial taxa (see Table 1). They also stratified the patients for KD treatment efficacy by standard definition of a decrease in seizure frequency of ≥50% as response and a lower seizure frequency reduction as non-response. Before starting KD there was no significant difference detected in the microbial communities between responders and non-responders. After six months on the diet, non-responders showed significantly higher relative abundance of several taxa belonging to the class Clostridia (*Clostridiales*, *Ruminococcaceae* and *Lachnospiraceae*) compared to the responder group. The authors conclude that their data offers potential targets for microbiome-based interventions to improve KD efficacy and reduce side effects but a larger cohort is needed to confirm these preliminary results.

Recently, whole metagenomic sequencing was used to analyse the faecal microbiome of 12 children with therapy-resistant epilepsy starting KD treatment and 11 controls [21]. Here, the genomes of the whole faecal microbial community were sequenced as opposed to the V3-V4 region of the 16S rRNA gene as in the previous studies. This method is less biased as it does not rely on PCR amplification prior to library preparation. It provides higher taxonomic resolution and can detect fungi and viruses. Most importantly, this approach enables functional profiling of the sequenced genes of the microbial community. In agreement with the studies mentioned above, no significant changes in alpha diversity were detected in the patients after three months on KD treatment. PCA indicated some shifts in both taxonomic and functional profiles after treatment. At phylum level Actinobacteria and Proteobacteria were significantly affected by the diet. Several Bifidobacteria were clearly diminished, most significantly *Bifidobacterium longum* and *Bifidobacterium adolescentis*, but also *Eubacterium rectale* and the genus *Dialister*. An increase in relative abundance was observed for *Escherichia coli*. Functional analysis revealed a significantly diminished carbohydrate metabolism encompassing several pathways including utilization of di- and oligosaccharides as well as

fermentation. Using functional shift decomposition [32] these changes could primarily be attributed to the decrease in relative abundance of *Bifidobacteria*. The increase in *E. coli* was associated with a decrease in many functions (see figure 4 in [21]) and an increase in the relative abundance of genes of the hemin transport system. *Bacteroides* have been associated with a long term diet rich in proteins and animal fats [33]. Although Lindefeldt et al. did not detect a significant enrichment of *Bacteroides* after KD as Zhang et al. did, a trend of induction was observed (median relative abundance 14.5% to 28.2%) in agreement with Xie et al. (median relative abundance 17.9% to 24.4%). Lindefeldt et al. found that *Bacteroides* were frequently associated with functional shifts in their dataset and thus might be important contributors to changes in the functional profile of the gut microbiota during KD.

These four studies investigating the gut microbial changes during KD in epilepsy show varying taxonomic changes. Different methods have been used, from selective RT-PCR and 16S rRNA gene sequencing to whole metagenomic sequencing. However, several caveats and limitations should be noted. The cohorts are all small, of different age and country of residence. They differ in the aetiology of the epilepsy, even within the cohorts [21,28,29]. Although all were adhering to a classic KD, there were differences in the source of dietary fats (either mainly derived from animals, plants or mixed) and the duration of the intervention. Thus, results are difficult to compare, and no taxonomic consensus can be established based on these studies. However, some common features can be noticed. Alpha diversity was not significantly changed after starting KD but several taxa were significantly reduced in relative abundance in the faecal samples and few were elevated (Table 1). Both Zhang et al. and Lindefeldt et al. detected a decrease in relative abundance of Actinobacteria during KD. Tagliabue et al. and Lindefeldt et al. found an increase in *Desulfovibrio* and *E. coli*, respectively. *Desulfovibrio* has been found enriched in patients with acute and chronic ulcerative colitis, subgroups of inflammatory bowel disease (IBD). Increased abundance of *E. coli* has been associated with IBD and colorectal cancer. In addition, iron acquisition has recently been shown to be critical for bacterial pathogenicity in biofilms from IBD patients [34]. Lindefeldt et al. found a concomitant accumulation of the relative abundance of genes of the hemin transport system during KD. Thus, the increased abundance of *Desulfovibrio* or *E. coli* during KD with a concomitant decrease in relative abundance of *Bifidobacteria* (Lindefeldt et al.) may indicate the potential of direct detrimental effects of KD on gut health in patients with epilepsy. However, in all three datasets using sequencing approaches, *Bacteroides* increased in relative abundance. This genus has been shown to be protective against IBD [35,36] and might explain the lack of evidence of an increased risk of IBD in patients even after long-term treatment with KD.

In order to elucidate the role of the intestinal microbiota for successful KD treatment of epilepsy we need larger cohorts enabling us to investigate correlations of specific microbes/groups of microbes and the potential functional relevance of these correlations to the anti-epileptic response to KD.

Multi-omics approaches could be applied to further delineate a potential mechanism by which gut microbiota may contribute to the anti-seizure effect of the diet. Here, animal models have provided us with some intriguing clues and will be discussed in the section below.

6. The role of the gut microbiota in epilepsy animal models

Animal models have been useful for studying the microbiota-gut-brain axis. Medel-Matus et al. demonstrated that stress-induced kindling epileptogenesis could be transferred from stressed rats to naïve (sham-stressed) Sprague-Dawley rats via FMTs, while the pro-epileptic effect of chronic stress was counteracted in stressed rats by FMTs from naïve rats [37]. These findings support a direct association between intestinal dysbiosis and chronic stress-induced epilepsy. Unfortunately, the authors did not sequence any of the transplanted faecal microbiota, so connections to specific microbial taxa cannot be made.

In a separate study, Olson et al. used two distinct epilepsy mouse models to investigate the effect of the ketogenic diet on the gut microbiota and to elucidate the microbiota-associated mechanisms of the diet's anti-seizure effect [38]. They could show that KD altered the murine gut microbiota and protected from both spontaneous tonic-clonic seizures due to a null mutation in the voltage-gated potassium channel Kv1.1 alpha subunit and acute electrically induced seizures by low-frequency (6-Hz) corneal stimulation, a standard model for drug-resistant epilepsy. Notably, they found that the anti-epileptic effect of KD was dependent on the gut microbiota. KD had no effect on seizure susceptibility in mice treated with antibiotics or reared germ-free and the anti-seizure effect could be transferred from KD-fed mice to mice on a control diet by an FMT. As *Akkermansia muciniphila* and *Parabacteroides* were increased in relative abundance in the gut microbiota of mice fed KD, Olson et al. tested whether enrichment of these bacteria in mice pre-treated with antibiotics could affect seizure susceptibility during a control diet. Neither *A. muciniphila* nor *P. merdae* and *P. distasonis* separately reduced seizures but a combination of these species did, suggesting important cross-feeding. Global metabolomics profiling of serum from mice on KD showed decreased levels of gamma-glutamyl amino acids compared to mice fed the control diet. This effect was diminished when the mice were pre-treated with broad-spectrum antibiotics and augmented when mice were colonized with *A. muciniphila, P. merdae* and *P. distasonis.* Pharmacological inhibition of gamma-glutamyltranspeptidase mimicked the anti-seizure effect of KD. These effects were accompanied by elevated hippocampal GABA/glutamate levels, which may contribute to seizure protection. These are exciting findings and it is now of importance to study whether similar mechanisms are involved in the anti-seizure effect of KD in patients. Animal and human studies have pointed out the critical role of GABAergic inhibition for normal hippocampal function and recent reports indicate involvement of GABAergic interneuron and glutamatergic networks at the initiation of seizures in the mesial temporal lobe [2,39].

7. The gut microbiome and antiepileptic drug therapy

The intestinal microbiota is increasingly recognized as an important factor in biotransformation of xenobiotics, including medications. For example, the treatment outcome of immunotherapeutic anticancer PD-1 blockade has been shown to depend on the composition of the patient's gut microbiota [40]. Zonisamide, an anticonvulsant drug, is metabolized to 2-sulfamoylacetylphenol by the intestinal microbiota [41]. Cecal fluids from rats, mice, hamsters, rabbits, and guinea pigs reduced zonisamide to 2-sulfamoylacetylphenol and treatment with antibiotics significantly inhibits the urinary and faecal excretion of this metabolite. Of the eight representatives of gut bacteria tested, *Clostridium sporogenes* and *Bifidobacterium bifidum* showed the highest reductive activity towards zonisamide under anaerobic conditions.

In addition, xenobiotics may directly impact the composition of the gut microbiota and treatment with certain drugs may induce dysbiosis. Antibiotics exhibit an inherent toxic activity against microbes and repetitive usage has been shown to induce dysbiosis and increase the risk of pathogen outgrowth such as *Clostridium difficile* [42,43]. In addition, Maier et al. showed that 24% of drugs across all classes with human targets inhibited the growth of at least one of 40 representative gut bacterial strains in vitro [44]. Subgroup N03A of the WHO controlled ATC (Anatomical Therapeutic Chemical) classification system of drugs comprises the anti-epileptic drugs (AEDs). 16 representative medicines of N03A were tested and none exhibited a clear antimicrobial effect. However, lamotrigine has been shown to inhibit ribosomal biogenesis in *E. coli* and thus, may inhibit its growth [45].

In summary, there are few indications of direct interactions of AEDs with the intestinal microbiome. However, more specific studies are needed to investigate the significance of such interactions for the treatment of epilepsy.

8. Outstanding questions

As discussed in this review, intestinal dysbiosis is associated with chronic stress-induced epilepsy in rats and members of the intestinal microbiota influence the anti-seizure effect of the ketogenic diet in mice. Recent studies in human cohorts suggest a dysbiosis in children with epilepsy but larger studies with age-matched controls are needed to confirm these indications. It may be possible that dysbiosis is more relevant in certain subtypes of epilepsy, e.g. stress-induced epilepsy. Thus, stratification for the aetiology may be crucial. If a dysbiosis can be confirmed, microbiota-targeted strategies may be developed as alternative treatments for epilepsy. These might aim at re-establishing a healthy microbial community using prebiotics, probiotics, or FMTs from healthy donors. Selectively targeting microbes associated with seizures through antibiotics or phage therapy might be an alternative option.

It is quite clear that the ketogenic diet has an impact on the intestinal microbiota. We now need to investigate whether and how these compositional and functional shifts are relevant for the anti-seizure effect of KD in patients, as it has been demonstrated in mice. Unravelling a mechanism possibly involving changes in systemic metabolites may open new avenues for treatment of epilepsy such as pharmacological inhibitors or analogues of these metabolites.

Today, about 25–30% of patients diagnosed with epilepsy are refractory to treatment with AEDs. Uncontrolled seizures may lead to cognitive deficits as memory and learning impairments, permanent brain dysfunction and an increased mortality. Furthermore, in patients with a clear seizure response to AEDs, side effects may limit their use [46]. Thus, patients with epilepsy are in need of improved alternative treatments and targeting the gut microbiota might be one option in the future.

9. Search strategy and selection criteria

Data for this Review were identified by searches of PubMed and references from relevant articles using the search terms “microbiome” and “epilepsy”.

Only articles published in English and up to January 25th, 2019 were included.

Declaration of competing interests

The authors have nothing to declare.

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