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Microbiota-gut-brain axis: A novel potential target of ketogenic diet for epilepsy

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Abstract

Ketogenic diet (KD) has been used to the control of seizure for 100 years because it was developed for the treatment of epilepsy in 1921. Based on current research on the microbiota-gut-brain axis to explore the new communication tool between gut bacteria and the brain and the progress of microbiota-gut-brain axis and KD for the treatment of epilepsy, the role of neurotransmitters adenosine and γ-aminobutyric acid in the epileptic brain, we propose that the balance between beneficial and harmful bacteria in the gut microbiota would be a promising target in the future to underlying the working mechanism of KD for epilepsy.

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Introduction

The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate protein diet, originally designed to mimic the metabolic effects of starvation by forcing the body to use its primary fat reserves [1]. In 1921, it was first developed for the treatment of epilepsy to control seizure activity [2]. Owing to the antiepileptic drug diphenylhydantoin (phenytoin) became available, the use of KD for epilepsy was decreased in 1938 [3]. However, in the 1990s, the KD treatment reattracted attention because it was shown to be effective for patients with drug-resistant epilepsy (DRE) and particular pediatric epilepsy syndromes [4]. Nowadays, the KD treatment for epilepsy has been used in a great number of countries worldwide [5]. The KD-based drug development strategy of epilepsy is still ongoing apart from that KD has been proved with positive effects in the management of epileptic seizures. Unfortunately, the precise mechanism has not been comprehensively understood, although a variety of hypotheses have been proposed and investigated [6–11]. Here, we would like to propose the microbiota-gut-brain axis (MGBA) hypothesis based on recent publications [12–16] and anticipate that it would be to serve as a novel promising target to provide a clearer answer on the working mechanism of KD for the treatment of epilepsy in the future.

The microbiota-gut-brain axis: a new communication way between gut bacteria and the brain

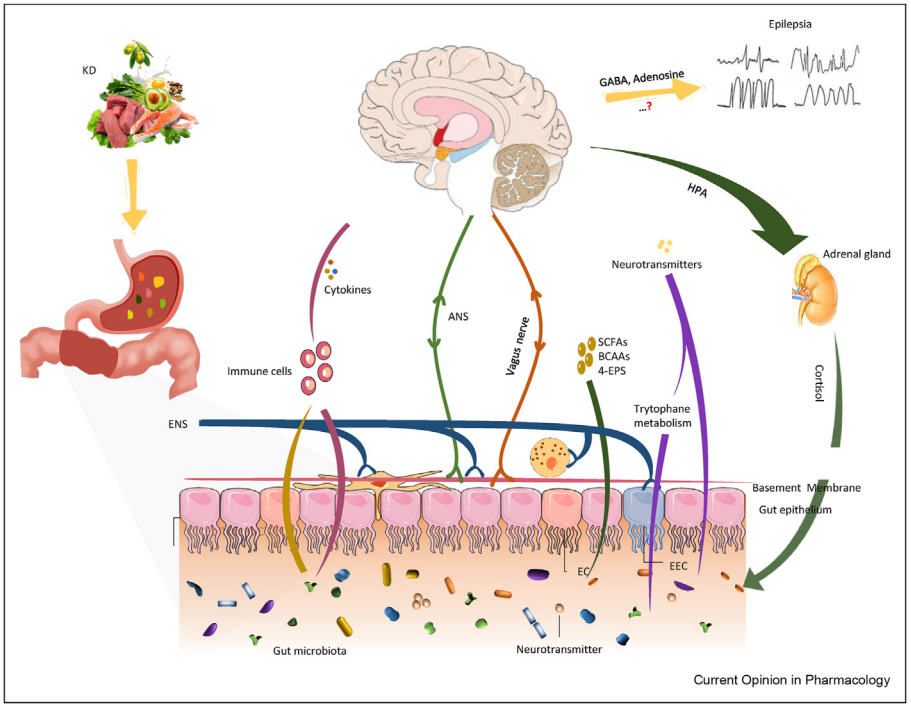
Increasing evidence from cross-sectional human studies demonstrated that changes in the diversity and relative abundances of the microbiota and microbial metabolites are related to neurologic and psychiatric disorders, including Parkinson's disease, Alzheimer's disease, autism spectrum disorders, epilepsy, and major depressive disorder, and so on. [17–22]. For instance, the decreased fecal microbial diversity, lower abundance of some beneficial bacterial taxa (*Eubacterium rectale*, *Bifidobacterium*, *Dialister*), and higher abundance of potentially pathogenic microbes (*Escherichia/Shigella*, *Bacteroides*, *Ruminococcus*) were found in patients with Alzheimer's disease [23–25]; the phylum Proteobacteria, including the genera of *Campylobacter*, *Delftia*, *Haemophilus*, *Lautropia*, *Neisseria*, was detected that they were higher in patients with idiopathic focal epilepsy than in healthy volunteers; the Fusobacteria phylum was found in 10.6% of the patients with epilepsy but not in the healthy volunteer [26].

Based on these studies and driven by the development of next-generation sequencing technologies in tandem with large cohort studies demonstrating the relationship between gut microbes and brain architecture in healthy subjects or disease states, the MGBA was established [27–29] and applied to uncover the pathological mechanism of epilepsy [30–33].

The MGBA refers to the network of connections involving multiple biological systems that allow bidirectional ('top–down' from the brain to the microbiota and 'bottom–up' from the microbiota to the brain) communication between gut bacteria and the brain. It is well-recognized that it plays a crucial

role in maintaining homeostasis of the gastrointestinal, central nervous, and microbial systems of the whole body [34–38]. The bidirectional routes of communication include the autonomic nervous system, the enteric nervous system (ENS), and the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis, the immune system, and metabolic pathways (Figure 1). Within the gut, gut microbes can produce bioactive peptides such as neurotransmitters γ-aminobutyric acid (GABA), noradrenaline, dopamine, and serotonin (5-hydroxytryptamine,5-HT), amino acids (tyramine and tryptophan), and microbial metabolites (short-chain fatty acids including acetate, butyrate, proprionate, and lactate; branched-chain amino acids and 4-ethylphenylsulfate). These metabolites can travel through portal circulation to interact with the host immune system, influence metabolism, and/or affect local neuronal cells of the ENS and afferent pathways of the vagus nerve that signal directly to the brain [39–41]. Additionally, the microbiota has the potential to impact levels of other neurotransmitters, including gasotransmitters, neuropeptides, histamine, steroids, endocannabinoids, and so on [42]. The gut microbiota can also influence gut barrier integrity that controls the passage of signaling molecules from the gut lumen to the lamina propria, which contain immune cells and terminal ends of ENS neurons, or to portal circulation. Gut barrier integrity can become disrupted in some neuropsychiatric conditions, such as anxiety, autism spectrum disorder, and depression. Within the nervous system, any stress could activate the HPA axis response that involves neurons of the hypothalamus that secrete hormones such as the corticotropin receptor hormone into the brain or the portal circulation, provoking the release of the adrenocorticotrophic hormone, which then initiates the synthesis and release of cortisol. Cortisol regulates neuroimmune signaling responses that, in turn, affect intestinal barrier integrity. Stress hormones, immune mediators, and CNS neurotransmitters can activate neuronal cells of the ENS and afferent pathways of the vagus nerve, which subsequently can change the gut environment and alter the microbiota composition [35–38,43–45].

Figure 1



MGBA-KD-Epilepsy. The MGBA and its potential communication way between gut bacteria and the brain in KD treatment for epilepsy. When the ketogenic food enters the gut, the changes of microbiota, metabolites, neurotransmitters, gut microenvironment, and so on will raise different message communications in the MGBA and would be a link to the seizure control via the main target GABA and adenosine in the brain. MGBA, microbiota-gut-brain axis; KD, ketogenic diet; ANS, autonomic nervous system; ENS, enteric nervous system; HPA, hypothalamic–pituitary–adrenal; EC, enterochromaffin cell; EEC, enteroendocrine cells; SCFAs, short-chain fatty acids; BCAAs, branched-chain amino acids; 4-EPS, 4-ethylphenyl-sulfate; GABA, gamma-aminobutyric acid; … ? means other potential mechanisms or targets are unknown apart from antioxidative stress, modulation of ion channel and neurotransmitter, antineuroinflammation, neuroprotection, and so on, and GABA, adenosine mentioned in this review.

Although the concept of the MGBA is relatively new, it is becoming increasingly accepted that the resident gut microbiota can raise considerable impact on different host behavior or functions [20,38,46,47]. And the constitution of the gut microbiome can also be influenced by diet; therefore, dietary therapy was shown to have a positive impact on a wide range of conditions via alteration of the gut microbiota or gut microbial metabolite production of short-chain fatty acid and trimethylamine [48–51].

The microbiota-gut-brain axis: a potential target to underlying the mechanism of ketogenic diet in epilepsy

KD has been reported to benefit more than one-third of patients with epilepsy [52] and especially confirmed to be an efficient treatment strategy for children who suffer from DRE [53]. The reduced average incidence and the decreased number of epileptic seizures were also found in both children and adolescents suffering from intractable epilepsy and receiving KD intervention [54]. However, we need to know why KD works well for the management of epilepsy. To the best of our knowledge, the hallmark features of KD treatment are the production of ketone bodies (principally, β-hydroxybutyrate, acetoacetate, and acetone) — products of fatty acid oxidation in the liver and reduced blood glucose levels. Administration of the KD first caused elevated levels of the ketone bodies β-hydroxybutyrate, acetoacetate, and acetone in the peripheral blood and urine. The increased serum ketones were identified to inhibit apoptosis and improve mitochondrial activity in the diseased brain [55]. KD-induced direct neuronal effects may get involved in the attenuation of oxidative stress and induction of protein expression of antioxidants [56], ATP-sensitive potassium channel modulation, modulation of neurotransmitter levels, such as glutamate, GABA, and monoamines, enhanced purinergic adenosine [57,58], increased brain-derived neurotrophic factor expression consequent to glycolytic restriction, and subsequently attenuation of neuroinflammation, as well as an expansion in bioenergetic reserves and stabilization of the neuronal membrane potential through improved mitochondrial function. Hence, it seems that beyond its utility as an anticonvulsant treatment, KD may also exert neuroprotective and antiepileptogenic properties, implying the clinical potential of the KD as a disease-modifying intervention [59]. It is worth to point out that owing to the crucial inhibitory of adenosine and GABA in the control of seizure, both of them would be considered the central target in the brain for the epilepsy management of KD. Olson et al. showed that when the symbiosis of KD-related *Akkermansia* and *Parabacteroides* was enriched and performed in non-KD diet mice, the epileptic protective effect of a KD was restored. The alterations in colonic lumenal, serum, and hippocampal metabolomic profiles were linked with seizure protection, including reductions in systemic gamma-glutamylated amino acids and elevated hippocampal GABA/glutamate levels. Bacterial cross-feeding reduced gamma−glutamyltranspeptidase activity, and inhibiting gamma-glutamylation promotes seizure protection *in vivo*. It demonstrated that gut microbiota is required for KD-mediated protection against acute epileptogenic seizures [12]. In addition, recent studies further showed that KD treated HT22 hippocampal murine neurons raised alternations of the energy metabolism and cellular lipids. Incubation of two important KD metabolites—beta-hydroxybutyrate (βHB) (the predominant ketone body) and decanoic acid (C10) with HT22 hippocampal murine neurons, the authors found significant elevation of Sirtuin 1 (SIRT1) (a group of seven nicotinamide adenine dinucleotide (NAD)-dependent enzymes and important regulators of energy metabolism) enzyme activity and an overall upregulation of the mitochondrial respiratory chain complexes [60] or significant alterations in cellular cholesterol, phospholipids, and sphingomyelin in hippocampal murine neurons [61]. However, these changes have not been confirmed by the *in vivo* study.

The previous evidence is linked to the mechanism of KD within the brain. However, what will happen in the gut microbiota when the KD treatment is provided. It has been recognized that what you eat would surely influence the gut microbiome [62]. The early study with the pediatric epilepsy population reported in 1976 presented that the KD increased *Bacteroides* and decreased *Firmicutes* and *Actinobacteria* in those who responded to KD, suggesting that KD is proposed to be fascinated as decreasing the bad bacteria in the gut and helping to restore the good bacteria [63]. One clinical observation in 20 children with DRE was performed to explore the features of gut microbiota, and it presented that after 6 months of treatment, 10 participants reported the microbial diversity, and the *Bacteroides* level of feces from the KD treatment group was much lower than their values at baseline together with an improvement in their clinical symptoms. However, in nonreactive groups, high levels of *Alistipes*, *Clostridium fusiform*, *Rumen coccidae*, *Richtellaceae*, and *Lacaceraceae* were observed. It implied that the intestinal flora community spectrum may be associated with KD treatment [64–66]. Another observational study found that three months of KD intervention for DRE did not cause alternations of *Firmicutes* and *Bacteroidetes* while significantly increased the species of *Desulfovibrio* [67]. But different changes of species were reported in another report from Sweden. Their design was that the 12 children with DRE with an average age of 7.7 years were given KD treatment for three months, although their parents were given a normal diet as a control. The analysis of fecal samples collected before and after the dietary intervention demonstrated that a significant decrease in the relative abundance of *Bifidobacteria*, *Dialister*, and *E. rectale* and an increase in *Escherichia coli*

were observed in the KD group [13]. All these studies demonstrated that KD treatment is a potential microbial-based dietary intervention and is a reasonable choice for patients with DRE, although the debate is still ongoing [68].

In addition, the immune factors that contribute to the underlying mechanism of KD for the treatment of epilepsy have just been investigated at the beginning. In the study of human beings, the children with epilepsy were recruited, and it was found that the KD not only improved the imbalances in the gut microbiome but also decreased pathogenic bacterial species and increased *Bacteroidetes*, particularly, the elevation of *Bacteroides* species are considered to be connected to the antiseizure effects of the KD treatment in that they regulate 6−17 interleukins in dendritic cells, which are potential immune factors to control seizure on patients with epilepsy involved in the gut-brain-axis [69]. Another new finding indicated that the alters of the gut microbiome induced by KD lead to decreased intestinal Th17 cells, which would be another novel evidence to reveal the immune involvement in the KD-induced MGBA mechanism [70].

Future work

To date, KD has been recognized as an important alternative therapy for the control of seizure. And the MGBA would be a novel promising target to explain the working mechanism of KD in the treatment of epilepsy. However, the following issues are still waiting for the answer. First, current data just presented the evidence on a few neurotransmitters in the brain, the immune factors, and the alternations of microbiota components in the gut, which are insufficient to provide a comprehensive answer to uncover the bidirectional regulation in the MGBA. In other words, what is the specific role of the autonomic nervous system, ENS and vagus nerve, HPA axis, immune system, metabolic pathways, and gut microbiota-related neurotransmitters, which contribute to the different components of the MGBA (Figure 1) in the KD-related MGBA for the treatment of epilepsy? It is still a big challenge and a long way to go. In addition, which way in the MGBA would be more important? And what is the interaction between different factors? For instance, the vagus nerve plays a crucial role in the MGBA communication, and it is also very important in the seizure control. However, the precise mechanism of vagus nerve in the MGBA to manage epilepsy still needs to be elucidated. Owing to the individual difference derived from age, gender, race, and so on exists, the impact of different gut microbiota or different brain responses on the KD-induced MGBA also needs to provide a clear answer. Based on current data and the drug target for the development of epilepsy, it seems that adenosine and GABA generated by KD in the brain (Figure 1) and the balance between good and bad bacteria in the gut microbiota would be also a promising target in the future to address the potential mechanism of KD for the treatment of epilepsy.

Conflict of interest statement

Nothing declared.

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