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MICROBIOTA GUT-BRAIN AXIS IN EPILEPSY

Anđela Dujmović
University of Zagreb, School of Medicine
0009-0000-8440-8422

Abstract

Epilepsy is one of the most common neurological disorders, affecting more than 70 million people globally, and a considerable percentage of cases are resistant to treatment. In addition, current treatments primarily manage the symptoms of the disease rather than its cause, highlighting the need to explore new strategies. A growing body of evidence highlights the impact of gut microbiota on epilepsy. This intriguing connection is mediated by bidirectional signaling through neural, endocrine, immune and humoral pathways—in other words, the gut-brain axis. It has been shown that the diversity and the composition of the gut microbiota are altered in epilepsy, stress and immune-inflammatory processes which affect seizure thresholds and neurological well-being. The ketogenic diet, which has long been used as a treatment, achieves its antiepileptic effects through the modulation of gut microbiota, while fecal microbiota transplantation is emerging as a potential new therapeutic approach. However, inconsistencies in research results and the question of the cause-effect relationship between gut-microbiota and epilepsy show the complexity of this interaction. More research is necessary to gain a better insight into the mechanisms involved in pathogenesis in order to develop new treatments that target the microbiota, with the aim of revolutionizing epilepsy management by treating its cause.

KEYWORDS: epilepsy, gastrointestinal microbiome, gut-brain axis, inflammation, ketogenic diet

INTRODUCTION

Epilepsy is a neurological disease that affects more than 50–70 million people worldwide, including 10.5 million children under the age of 15.[1] Around 80% of patients live in low- and middle-income countries. Additionally, approximately 33% of patients suffer from refractory epilepsy, placing a tremendous burden on global health and finances.[2–4] It is defined by the propensity for recurrent, unprovoked epileptic seizures.[5] Seizures are transient clinical manifestations arising from abnormal, paroxysmal changes in the electrical activity of neurons and are linked to an imbalance between excitatory and inhibitory brain networks.[6] Glial cells also contribute to seizure generation by modulating neural function and maintaining the balance of ions and neurotransmitters, specifically glutamate and gamma-aminobutyric acid (GABA).[7] The causes of seizure generation can be categorized into six groups: structural, genetic, infectious, metabolic, immune and neurodegenerative. These categories often overlap, with genetic factors potentially influencing all cases of epilepsy.[8] Moreover, since epilepsy is a disease with high morbidity and mortality rates, and existing medications only address the symptoms rather than the underlying causes, scientists have been motivated to seek potential new solutions to these problems.[6] Consequently, research has demonstrated an association between gut microbiota and epilepsy.[1] Exploring this interaction could reveal ways in which gut microbiota influences the pathogenesis of epilepsy, leading to novel therapeutic targets and the development of customized preventive strategies.

THE POTENTIAL RELATIONSHIP BETWEEN THE GUT MICROBIOTA AND EPILEPSY

The gut-brain axis (GBA) involves two-way communication between the central nervous system (CNS) and the enteric nervous system, connecting the brain's emotional and cognitive regions with intestinal functions.[9] Recent research has highlighted the crucial role of gut microbiota in these interactions. This bidirectional relationship allows signals to travel from the gut microbiota to the brain and vice versa, through neural, endocrine, immune, and humoral pathways.[9] Abnormal gut microbiota can disrupt CNS homeostasis and contribute to the pathogenesis of neurological diseases, including epilepsy.[10] Interestingly, gastrointestinal symptoms, such as abdominal pain or diarrhea, may be the first or only obvious symptoms in individuals with epilepsy and can sometimes even lead to misdiagnoses.[11] Additionally, patients with inflammatory bowel disease have an increased risk of suffering from epilepsy.[12]

Although the GBA is not a novelty in science, interest in gaining new insights does not wane.[13] Studies have shown inconsistent results regarding the diversity of gut microbiota in epilepsy patients. Some studies report lower microbiota diversity in epilepsy patients compared to controls,[13–15] while others found increased diversity in drug-resistant epilepsy patients.[16] Regarding the composition of intestinal microbiota in epilepsy, most studies report an increased abundance of Firmicutes and a decreased abundance of Bacteroidetes.[15,16,17] Certain bacterial genera, such as *Campylobacter*, *Delftia*, *Haemophilus*, *Lautropia*, and *Neisseria*, are more abundant in epilepsy patients.[18] On the other hand, the abundance of *Bifidobacteria* and *Lactobacillus* correlates with fewer seizures.[16]

STRESS-INDUCED CHANGES IN EPILEPSY

Nowadays, chronic stress is the main culprit for a wide range of diseases. Correspondingly, it can influence epilepsy susceptibility. The hypothalamic-pituitary-adrenal (HPA) axis is a key regulatory system in the stress response.[19] Different hormones within the HPA axis have distinct effect on seizures: glucocorticoid levels are elevated in epilepsy patients,[19] while deoxycorticosterone exhibits beneficial effects.[20] Along those lines, corticotropin-releasing hormone (CRH) and corticosterone promote the signaling of excitatory neurotransmitters like glutamate, which can induce seizures.[20–22] Recent research has revealed a correlation between gut microbiota and the HPA axis. A study by Vodička et al. studied the effects of the chronic stress-microbiota interaction on HPA axis activity and on the expression of colonic corticotropin-releasing hormone (CRH) system, cytokines and 11β-hydroxysteroid dehydrogenase type 1 (11HSD1), an enzyme that determines locally produced glucocorticoids. Using specific pathogen-free (SPF) and germ-free (GF) BALB/c mice, they showed that the microbiota modulates emotional behavior in social conflicts and the response of the HPA axis, colon and mesenteric lymph nodes (MLN) to chronic psychosocial stress. For example, chronic psychosocial stress in specific pathogen-free mice upregulates colonic CRH and urocortin 2 expression, while downregulating cytokine expression compared to germ-free mice.[23] Chronic stress also alters gene expression in rat colon epithelial cells, promoting chromatin remodeling, barrier dysfunction, and inflammation.[24] Nevertheless, further investigation is required to fully understand the mechanisms of this interplay in order to develop microbiota-targeted therapies for clinical application.

GUT MICROBIOTA-MEDIATED IMMUNE RESPONSE IN EPILEPSY PATHOLOGY

A growing body of evidence suggests that gut microbiota, immune responses, and epilepsy are interconnected. Occludin and claudin are key proteins responsible for maintaining the integrity of the intestinal mucosal barrier (IMB) and the blood-brain barrier (BBB).[25] The gut microbiota plays a significant role in regulating their expression.[26] When integrity is disrupted, the permeability of these barriers increases, allowing pathogenic microorganisms and toxins to escape from the intestinal tract.[25] Subsequently, there is a significant influx of immune cells and inflammatory factors into the CNS, ultimately triggering seizures through interactions with astrocytes and microglia.[25,27,28] For example, research showed increased BBB permeability and inflammation in germ-free or antibiotic-treated mice, correlating with altered occludin and claudin expression.[26,29]

Specific gut bacteria, such as those in the Bacteroidetes phylum, influence Th17 cells and IL-17 secretion, which are crucial for the adaptive immune response. Elevated IL-17 levels in the cerebrospinal fluid and blood of epilepsy patients correlate with increased seizure frequency and severity.[30] Additionally, studies utilizing rodent models have demonstrated heightened TNF-α and IL-1β levels after the injection of bacterial lipopolysaccharides. This led to a lowering of the seizure threshold in chemically or electrically induced seizures.[31,32] Collectively, these findings suggest that gut microbiota influences epilepsy through immune-inflammatory pathways and barrier integrity. Further research is warranted to explore these mechanisms in order to develop new therapeutic methods.

TREATMENT STRATEGIES

The ketogenic diet (KD) was first introduced in the 1920s after Dr. Russell Wilder observed that absolute fasting halted seizures.[33] As a dietary intervention, the KD mimics the effects of fasting through a high-fat, moderate-protein, and low-carbohydrate composition. This approach induces ketosis, providing the brain with ketones as an alternative energy source to glucose. Recent research has demonstrated that KD treatment leads to an increased abundance of *Akkermansia* and *Parabacteroides*.[10,15,34] The beneficial effects of *Akkermansia muciniphila* have been linked to the production of short-chain fatty acids following KD consumption.[35] The SCA production has been shown to enhance mitochondrial function, reduce oxidative stress, and increase seizure thresholds.[26,29] In contrast, the abundance of *Bifidobacteria* decreases after KD treatment, despite their known antiseptic properties.[36] Scientists speculate that the antiepileptic role of KD treatment depends on gut microbiota. For instance, germ-free mice with epilepsy exhibit resistance to KD treatment.[10] However, *Akkermasia*- and *Parabacteroides*-treated epileptic mice show reduction in the frequency and severity of seizures as indicated by Olson et al.[10] The above study has confirmed that the gut microbiota acts as an essential link in the antiepileptic effect of KD.

In addition to KD, fecal microbiota transplantation (FMT) is gaining recognition as an effective method for restoring gut microbiota. FMT is a medical procedure characterized by introducing fecal matter obtained from healthy donors into recipients' gut, with the primary aim of addressing gut dysbiosis associated with various diseases[37] including epilepsy, *Clostridium difficile* infection, inflammatory bowel disease, and related disorders.[10,38,39] One case study by He et al reported significant improvements in a patient with Crohn's disease and refractory epilepsy following three consecutive FMT procedures. The patient's Crohn's disease activity index dropped substantially from 361 to 131, and seizures were fully controlled without anti-seizure medications for 20 months post-FMT. [40] This case is particularly intriguing due to the potential autoimmune link between Crohn's disease and epilepsy. While a single case does not provide conclusive evidence, it highlights the potential of this link and supports the need for deeper investigation and broader scientific exploration.

These findings demonstrate the influence of intestinal flora on epilepsy, highlighting the microbiota as a potential target in the development of new therapeutic strategies. Extensive research continues on this topic, as refractory epilepsy remains one of the most significant challenges in the field.

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CONCLUSION

Emerging evidence from animal models and clinical studies emphasizes the significant role of gut microbiota in epilepsy. The gut microbiota contributes to seizures through various pathways, including visceral, sensory, endocrine, and immune mechanisms, while also influencing therapeutic outcomes. However, the specific microbiota involved in epileptogenesis remains unknown, and current research has provided inconsistent results. It remains unclear whether alterations in gut microbiota cause epilepsy or are simply a consequence of the condition. This uncertainty highlights the challenges in developing microbiota-targeted therapies and the need for further research. Understanding the GBA offers an opportunity for novel interventions, potentially shifting epilepsy management from symptom control to addressing underlying causes.

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CRIJEVNA MIKROBIOTA I CRIJEVNO-MOŽDANA OS U EPILEPSIJI

Sažetak

Epilepsija je jedan od najčešćih neuroloških poremećaja koji zahvaća više od 70 milijuna ljudi diljem svijeta, a znatan udio slučajeva pokazuje rezistenciju na terapiju. Današnje liječenje primarno djeluje na simptome bolesti umjesto na uzrok, zbog čega je potrebno istražiti nove strategije. Sve je više dokaza koji naglašavaju utjecaj crijevne mikrobiote na epilepsiju. Ova intrigantna veza posredovana je dvosmjernim signaliziranjem kroz neuralne, endokrine, imunološke i humoralne puteve odnosno, putem crijevno-moždane osi. Dokazano je da su raznolikost i sastav crijevne mikrobiote promijenjeni u epilepsiji, stresu i imunološko-upalnim procesima što posljedično povisuje prag okidanja epileptičkog napadaja. Ketogena dijeta se već dugo koristi u liječenju epilepsije, a svoje antiepileptičke učinke postiže modulacijom crijevne mikrobiote. Potencijalni novi terapijski pristup je transplantacija fekalne mikrobiote. Međutim, razvijanje novih terapijskih pristupa je zahtjevno jer su rezultati mnogih istraživanja nedosljedni i jer se ne zna uzročno-posljedična povezanost crijevne mikrobiote i epilepsije. To dokazuje da je njihova povezanost kompleksna. Potrebna su dodatna istraživanja kako bi se detaljnije objasnile nove metode liječenja koje bi bile usmjerene na mikrobiotu i potencijalno bi mogle revolucionirati liječenje epilepsije.

KLJUČNE RIJEČI: crijevna mikrobiota, crijevno-moždana os, epilepsija, ketogena dijeta, upala