ISSN 2221-2582

UDC 616.34-008.87+579.67+616.853+577.175.82+579.67+577.18+615.33
DOI: 10.56871/CmN-W.2024.56.72.009

ROLE OF INTESTINAL MICROBIOTA IN THE GENESIS OF EPILEPSY

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For citation: Bogdanova NM, Kravtsova KA. Role of intestinal microbiota in the genesis of epilepsy. Children's Medicine of the North-West. 2024;12(2):102–117. DOI: https://doi.org/10.56871/CmN-W.2024.56.72.009

Received: 28.12.2023 **Revised: 04.03.2024** **Accepted: 05.06.2024**

Abstract. It is generally recognized that the health and well-being of a macroorganism depends on the adequate functioning of the gut microbiota and brain. It is noted that the gut microbiota is involved in the formation of brain functions through various pathways and systems, including the CNS. In such a situation, it is legitimate to assume that the microbiota may be a trigger in the development of epilepsy. Statistically significant differences in the microbial composition of feces between patients with epilepsy and healthy people were revealed. Epilepsy is a chronic brain disease of various etiologies. Moreover, in 40–60% of patients, the cause of this ailment remains unknown. Diversification of the gut microbial landscape has been shown to be accompanied by activation of epileptic paroxysms. However, the composition and structure of the intestinal microcosm is so complex and insufficiently studied that it is almost impossible to single out certain bacteria as the most "useful" or "dangerous" in epilepsy. It is assumed that excessive local synchronization of the bielectric activity of the brain is due to minimal chronic inflammation and leaky bowel syndrome with an imbalance in signal transmission along the brain-intestine axis. The main method of treating epileptic paroxysms is the prescription of pharmaceuticals. At the same time, in every third patient with epilepsy, refractory epilepsy occurs. The study of the species diversity, composition and function of the intestinal microbiota in patients with epilepsy, but with somewhat contradictory results, indicate the presence of intestinal dysbiosis in them and their potential value in the diagnosis and control of epilepsy treatment, especially in its refractory form.

Key words: *microbiota, epilepsy, paroxysm, nervous system, intestinal metabolites, neurotransmitter, short-chain fatty acids, ketogenic diet, probiotic, antibiotic*

РОЛЬ КИШЕЧНОЙ МИКРОБИОТЫ В ГЕНЕЗЕ ЭПИЛЕПСИИ

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Для цитирования: Богданова Н.М., Кравцова К.А. Роль кишечной микробиоты в генезе эпилепсии // Children's Medicine of the North-West. 2024. Т. 12. № 2. С. 102–117. DOI: https://doi.org/10.56871/CmN-W.2024.56.72.009

Поступила: 28.12.2023 **Одобрена: 04.03.2024** **Принята к печати: 05.06.2024**

Резюме. Общепризнанно, что здоровье и благополучие макроорганизма зависят от адекватного функционирования кишечной микробиоты и мозга. Отмечено, что кишечная микробиота принимает участие в формировании функций головного мозга через различные пути и системы, включая центральную нервную систему. В такой ситуации правомочно предположить, что микробиота может быть триггером в развитии эпилепсии. Выявлены статистически значимые различия в микробном составе фекалий между больными эпилепсией и здоровыми людьми. Эпилепсия — хроническое заболевание головного мозга различной этиологии, причем у 40–60% больных причина данного недуга остается неизвестна. Показано, что диверсификация микробного пейзажа кишечника сопровождается активацией эпилептических пароксизмов. Однако состав и структура кишечного микромира настолько сложны и недостаточно изучены, что выделить определенные бактерии как наиболее «полезные» или «опасные» при эпилепсии практически невозможно. Предполагается, что чрезмерная локальная синхронизация биэлектрической активности мозга обусловлена минимальным хроническим воспалением и синдромом «дырявого кишечника» с разбалансировкой передачи сигналов по

оси мозг–кишка. Основной метод лечения эпилептических пароксизмов — назначение фармацевтических препаратов. При этом у каждого третьего пациента с эпилепсией имеет место рефрактерная эпилепсия. Изучение видового разнообразия, состава и функции кишечной микробиоты у пациентов с эпилепсией, но с несколько противоречивыми результатами, указывают на наличие у них кишечного дисбиоза и на их потенциальную ценность в диагностике и контроле лечения эпилепсии, особенно при ее рефрактерной форме.

Ключевые слова: *микробиота, эпилепсия, пароксизм, нервная система, кишечные метаболиты, нейротрансмиттер, короткоцепочечные жирные кислоты, кетогенная диета, пробиотик, антибиотик*

INTRODUCTION

The gut microbiome (GMB) is a group of microorganisms that includes many prokaryotes (bacteria), eukaryotic microorganisms (such as fungi and protozoa), archaea and viruses that associate with the macroorganism [1–3].

In the modern world, the relationship of the macroorganism with gut microbes is the result of evolution over thousands of generations. Over millions of years, evolution has acted not only on our 23,000 genes, but also on nearly 4 million genes (both human and microbial) that are present in and on our bodies [4]. Metagenomic analyses have allowed the identification of seven dominant types of bacteria that contaminate the human gastrointestinal (GI) tract: *Firmicutes*, *Bacteroidetes*, *Actinobacteria, Proteobacteria, Fusobacteria, Verrucomicrobia* and *Cyanobacteria,* among which *Bacteroidetes* and *Firmicutes* account for more than 90% [5–7].

The study of the ontogenesis of the child's nervous system confirms the parallel development of the gut microbiome, the immune response and the central nervous system (CNS). The cognitive function of a child at the age of 2 years has been shown to be highly dependent on the qualitative composition of his or her gut microbiota in the first year of life [8].

In infancy, the brain has enormous metabolic capacity and activity. Comprising 5–10% of total body weight, the brain is responsible for almost 50% of the body's basal metabolic energy and is therefore particularly sensitive to reduced energy intake [9]. Due to the ability of microbial communities to control the amount of energy input, they can control the development of the nervous system during the first years of an infant's life.

Thus, the parallel maturation of the microbiome and CNS during the first stages of life suggests that the physiological development of the child's nervous system is possible if microbiome processes are optimised [10].

MICROBIOTA–GUT–BRAIN AXIS

OIt is generally recognised that the health and well-being of the macroorganism depend on the optimal functioning of the GMB and the brain. A number of experimental and clinical studies have shown that any negative impact on either the microbiota or the brain simultaneously results in damage to the functions of the two systems: the GI tract and the CNS. In other words, there is a bidirectional co-operation of the GMB with the brain, the so-called brain-gut-microbiota (BGM) axis [11–14], which is confirmed by the latest research on the microcosm of *Homo sapiens*.

It has been shown that changes in the structure of the gut microbiota lead to the development of not only intestinal diseases, metabolic disorders, allergic and autoimmune pathology, but also a number of neurological disorders, including neurodegenerative diseases (such as Parkinson's disease, Alzheimer's disease, multiple sclerosis), autism, depression, schizophrenia, and epilepsy. It has been observed that patients with epilepsy have a high incidence of digestive symptoms, and patients with inflammatory bowel disease (IBD) have a high predisposition to epilepsy [15–17]. In addition, statistically significant differences in faecal microbial composition have been found between epilepsy patients and healthy controls, as well as between patients with all forms of epilepsy before and after inclusion of ketogenic diet therapy [18–24].

Much of our understanding of interactions along the BGM axis is based on metagenomics and metabolomics data from experimental studies [25].

The complex bidirectional communications that link GMB to the brain encompass mitochondrial function, axis, hypothalamic-pituitary-adrenal, and autonomic, neurohumoral, enteroendocrine and immunomodulatory pathways. For example, it has been noted that GMB is able to modulate the enteric nervous system (ENS) and neuronal network through activation of the vagus nerve, immune and APUD system cells [8], as well as due to the synthesis and perception of pro- and anti-inflammatory cytokines, neurotransmitters (serotonin and GABA) and products of microbial metabolism such as secondary bile acids and short-chain fatty acids (SCFAs) [26]. The whole arsenal presented affects neuronal messages

and appears to regulate brain functions and therefore determines cognitive performance, behaviour, mood, presence of anxiety and/or depression [25, 27–29].

Experimental work performed on mouse models demonstrates the relationship of the gut microbiome with the levels of key neurotransmitters and single neuroreceptors in the brain. Gnotobionts (GF) show a drop in brain-derived neurotrophic factor (BDNF) expression, predominantly in the hippocampus [30]. Conversely, rodent models with a healthy microbiota show increased expression of BDNF, which is important for mediating neural stem cell proliferation [31]. Feeding GF mice with the probiotic *Lactobacillus rhamnosus* (JB-1) regionally and differentially modifies GABA receptor expression in them: there is an increase in expression in cortical regions and a decrease in prefrontal cortex and amygdala. These transformations in the expression of central GABA receptors are accompanied by changes in behaviour associated with anxiety and depression [25].

Other experimental studies have revealed a connection between GMB and the expression of N-methyl-D-aspartate (NMDA) [30], serotonin 1A [25] and tryptophan [13] receptors. The first receptor mediates the effects of the excitatory neurotransmitter glutamate [31], while the second and third mediate the effects of the inhibitory GABA.

In recent years, an aberrant microbiota profile has been shown to be associated with autism spectrum disorders, chronic pain, mood defects and affect development, and neurodegenerative diseases [12, 31–36]. This is clearly supported by scientific research. For example, transplantation of faecal microbiota (TFM) into GF mice from patients with Parkinson's disease caused motor deficits and neuroinflammation in rodents — two major features of Parkinson's disease [37]. In the GMB structure of patients with Alzheimer's disease compared to healthy individuals, a decrease in the level of microorganisms of *Firmicutes* phyla and *Bifidobacterium* genus and proliferative growth of *Bacteroidetes* phyla were observed [38]. In the faeces of patients with multiple sclerosis, researchers found high levels of *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* [39].

Considering that the gut microbiota is involved in the formation of brain function through various pathways and systems, including the CNS, it is reasonable to assume that it may also be involved in the development of the epilepsy [40].

GUT MICROBIOM AND EPILEPSY

Epilepsy is a chronic polyetiological brain disease characterised by recurrent unprovoked (or reflex) seizures of motor, autonomic, sensory and mental disorders resulting from excessive neuronal discharges [41–43].

According to data published in the Lancet (2019), epilepsy affects more than 70 million people around the world [44]. The debut of the disease is mainly occurr in childhood (about 75% of all episodes) [45]. The mechanisms of paroxysms are quite complex and the etiological factors are multifaceted. Although still in 40–60% of patients the cause of epilepsy remains unknown [41, 46, 47]. Is it correct to identify any seizures with epilepsy in such a situation? Certainly not, since situationally determined seizures "theoretically" have significant differences from epileptic seizures.

Firstly, epileptic paroxysms in most cases have a recurrent, predominantly stereotyped character. Moreover, their recurrence occurs without provocation by external and internal stimuli. However, as always, there are exceptions to the rule, and in some forms of the disease there is polymorphism of seizures.

Secondly, in epileptic recurrent seizures, nerve cell death occurs in the brain, whereas in situational seizures there is more often brain oedema without neuronal death.

Thirdly, it is the presence on the electroencephalogram of specific changes in epilepsy. Although, if the patient has rare paroxysms, electrical markers of diagnosis may be absent. And epileptiform discharges on the EEG can occur in patients without seizures.

However, in clinical practice, diagnosis of epilepsy is often a difficult problem that must be solved because patients with epilepsy have an increased risk of mental illness, which increases their disability and mortality. And the presence of uncontrolled paroxysms can lead to impaired memory, cognitive function and intelligence, delayed psychomotor development and even brain death.

The most popular way to treat epileptic paroxysms is to prescribe pharmaceutical drugs. However, one in three patients with epilepsy cannot be treated with anticonvulsant therapy, i.e. they have refractory (resistant) epilepsy [48]. The International Antiepileptic League (ILAE) task force defined drug resistance as "the failure of adequate trials of two tolerated, appropriately selected and used antiepileptic drug regimens (whether as monotherapy or in combination) to achieve sustained seizure-free epilepsy" [49].

Alternative therapies: ketogenic diet (KD), neurostimulation and surgery, which are resorted to in resistant epilepsy, do not always achieve a positive outcome. In order to justify the inclusion of new, more promising treatment regimens in epilepsy

management protocols, it is necessary to carefully consider the various etiopathogenetic mechanisms that may trigger the development of this disorder. Currently, scientists consider the gut microbiota as a possible trigger factor in the genesis of epilepsy [40].

The relationship of distortion of GMB composition has been established in models of epilepsy and in clinical studies. Rats with colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) have been shown to have increased susceptibility to pentylenetetrazole(PTZ)-induced epilepsy [50]. In a mouse model of PTZ-induced seizures, intestinal inflammation increases seizure activity and reduces the efficacy of antiepileptic drugs (AED). In turn, alleviation of inflammation induces specific antiepileptic effects [14]. Thus, a reversible inflammatory response was observed in the hippocampus of rats treated with TNBS, characterised by microglia activation and an increase in tumour necrosis factor alpha (TNFα). This suggests that gut inflammation increases CNS excitability and inversion of inflammation [50].

There is evidence that stress is able to rearrange the microbiocenosis. Simulated stress in rats provokes epileptic seizures and causes transformation of the gut microbiota [51, 52]. Transplantation of faecal contents of stressed rats to non-stressed animals generated in the latter an increased frequency and duration of seizures after basolateral amygdala excitation. At the same time, the inoculation of gut microbiota into mice with simulated stress from subjects not experiencing the disease prevented the convulsive effects of chronic stress in the former [52].

A recent study in mice found that intestinal inflammation increases pharmacologically induced seizure readiness [17], and administration of anti-inflammatory drugs reduced susceptibility to paroxysms and restored the efficacy of antiepileptic drugs.

In WAG/Rij rats of a genetic model of absent epilepsy at one month of age and before the onset of paroxysms, a change in GMB with a lower *Bacteroidetes/Firmicutes* ratio was detected. In 4 months after the debut of absences, an inverse correlation was recorded: an increase in the frequency of seizures was accompanied by a further decrease in the *Bacteroidetes/Firmicutes* ratio towards an increase in *Firmicutes* phyla microorganisms [22].

In another experiment, it was observed that gut microbiota infection triggered by Gram-negative bacteria, such as *Bacteroides fragilisor* representative of the normal colon microbiota of humans, can lead to the formation of cerebral cavernous malformations (CCM), structural abnormalities in brain capillaries that contribute to stroke and seizures in genetically predisposed mice [53]. Gnotobiont mice do not develop such cerebral abnormalities.

Analysis of the faecal microbiota by 16S ribosomal DNA sequencing in patients with pharmacoresistant epilepsy (PRE) and healthy individuals, including children aged 1 to 4 years, identified qualitative and quantitative abnormalities in GMB composition in the former relative to the latter. Patients with PRE had a decrease in the species diversity of gut microbiota with a predominance of *Firmicutes* phyla microorganisms, while in healthy individuals *Bacteroidetes* phyla were dominant [54].

In the work A. Peng (2018) it is noted that the number of microorganisms of the *Bacteroidetes* phyla and *Actinobacteria* class is suppressed in patients with the PRE compared to healthy controls, while the number of representatives of the *Firmicutes* phyla increases [8, 54]. The authors also revealed the dissimilarity of intestinal microcosm patterns in patients with the PRE and drug-responsive form of epilepsy. In the first group (n=49) compared to the second group (n=42), there was an increase in α-diversity, i.e., the diversity in the number of microorganisms within the family, abundance of rare bacteria, mainly belonging to the phylum *Firmicutes.* The microbial profile at the phylum level of patients with drug-sensitive epilepsy resembled that of healthy individuals: microorganisms of the phylum *Bacteroidetes* were dominant. In addition, an inverse correlation between the titre of bifidobacteria and lactobacilli in faecal samples and the frequency of seizures in patients was established, i.e. intensive growth of commensal microorganisms was accompanied by a reduction in the number of seizures [8].

Another picture of the microbial landscape described in the study of X. Gong (2020). In patients with PRE compared to healthy controls, there was a decrease in *Bacteroidetes* and *Proteobacteria* phyla, as well as enrichment of bacterial taxa of *Actinobacteria* and *Verrucomicrobia* phyla and other bacteria at the level of genus and family *Nitrospirae* and at the level of genera *Blautia*, *Bifidobacterium, Subdoligranulum, Dialister* and *Anaerostipes* ($p < 0.05$). Which means that specific strains of intestinal commensals are transformed according to clinical phenotypes, which may serve as a potential biomarker for disease diagnosis [18].

B. Şafak et al. (2020) performed a contrast analysis of the faecal microbiome between patients with idiopathic focal epilepsy (n=30) and a group of healthy individuals (n=10) and found that *Proteobacteria* and *Fusobacteria*, which can cause autoimmune diseases, were present in significantly higher titre in the first group compared to the

second. Bacteroidetes and *Actinobacteria*, which have positive effects on the immune system, were present in lower titre in the first group [19]. This work confirms the role of autoimmune mechanisms and inflammation in the etiology of epilepsy.

In a study led by K. Lee (2020), 17 species of bacteria were identified in the group of patients with epilepsy, while in the group of healthy people 18 species were identified [20]. E*nterococcus faecium, Bifidobacterium longum,* and *Eggerthella lenta* were found to be the strongest potential biomarkers in a group of patients with untreatable epilepsy [20].

The study of the α- and β-diversity in adult patients in both the PRE (n=23) and drug-responsive epilepsy (DRE) groups (n=21) showed no significant differences. Some differences in the composition of the gut microbiota were associated with the patients' response to AED. Thus, *Bacteroides Finegoldii* and *Ruminococcus* were significantly more frequently recorded in the DRE group compared to the PRE. Besides, the dissimilarity of representatives of the microcosm took place depending on the data of instrumental diagnostic methods. In individuals with normal magnetic resonance imaging (MRI) pattern *B. finegoldii* dominated, and in patients with normal EEG pattern — *Bifidobacterium* dominated [21].

Thus, studies of GMB species diversity, composition and function in patients with epilepsy, but with somewhat contradictory results, indicate the presence of intestinal dysbiosis and their potential value in the diagnosis and management of epilepsy, especially in its refractory form. However, the presented reorganisation of GMB in patients with epilepsy cannot be completely consistent given the many variables affecting the gut microbiome, namely differences in study design, age of patients, diet and living conditions. For this reason, sufficiently large samples with reasonably controlled variables are needed to obtain more accurate results.

BASIC MECHANISMS OF THE RELATIONSHIP BETWEEN GUT MICROBIOM AND EPILEPSY

As it was noted above, changes in the GMB structure are accompanied by activation of epileptic paroxysms. This most likely occurs as a result of the development of the "leaky gut" syndrome. Increased permeability of the epithelial barrier allows bacteria, toxic metabolites, endo- and exotoxins, and small molecules (inflammatory cytokines and excitatory amino acids) to enter the bloodstream, alter the integrity of the blood-brain barrier, and negatively affect the brain [55, 56]. Thus, when the integrity of these two barriers is compromised, immune cells and compounds released by microbiota enter the brain and disrupt the balance between excitatory and inhibitory neurotransmitters, provoking the development of seizures.

Gut microbes metabolise alimentary tryptophan into aryl hydrocarbon receptor agonists and interact with its receptor to control microglia activation and growth factor expression (TGFα and VEGF-B vascular growth factor), thereby modulating the pathogenic activity of astrocytes [57, 58]. Inflammatory cytokines and chemokines released by astrocytes enhance microglia activity, including phagocytosis migration of apoptotic cells and synapse contraction [59]. Contact between astrocytes and microglia increases the production of pro-inflammatory cytokines with infiltration of immune cells and subsequent chronic neuroinflammation, as well as increased blood-brain barrier permeability [60].

Microglia morphology was altered in gnotobiont- or antibiotic-treated animals. Defects in maturation, activation and differentiation of neurons were detected, which led to an inadequate immune response to various pathogens. These disorders could be eliminated only after recolonisation with microbiota [61].

In addition to glial cells, peripheral immune cells are involved in the establishment of epileptic paroxysms: T cells and monocytes that transit into brain tissue from the intestine [62]. The exact mechanism of this transit is not fully established.

GMB may provoke epilepsy through an innate immune response. Blood-brain barrier permeability has been shown to increase throughout the life of GF mice, and this is due to reduced expression of *occludin* and *claudin-5* proteins in the intestinal endothelium [63]. Intestinal dysbiosis firstly reduces claudin production and expands the permeability of the intestinal mucosa with migration of microorganisms, their metabolites and toxins from the intestinal lumen [64], and secondly, it reduces the amount of SCFAs, exacerbating blood-brain barrier permeability and generating neuroinflammation [65].

Peptidoglycan (PGN) is a component of bacterial cell wall, which is mainly present in human GI tract. But PGN is also found in brain microglia from patients with chronic encephalitis [66]. That is, PGN can move from the gut to the CNS, contributing to chronic inflammation and paroxysms.

GMB contributes to epilepsy by inducing and adaptive immunity by synthesising cytokines that penetrate the brain through the gut mucosa and the blood-brain barrier and activate immune cells in the brain to participate in the immune response. For example, *IL-17* produced by Th17 cells can be

modulated by specific phyla of the gut microbiota, primarily by *Bacteroidetes* [8, 67, 68]. It has been shown that in patients with epilepsy, both in cerebrospinal fluid and peripheral blood, *IL-17* levels are higher than in controls and have a direct correlation with the frequency and severity of seizures [69–72].

Intestinal metabolites such as SCFAs are able to influence immunoglobulin synthesis and secretion by regulating B-lymphocyte differentiation [73, 74]. The absence of a commensal microbiota suppresses *IgA* and *IgG1* formation and induces *IgE*, which increases susceptibility to disease [75, 76].

Consequently, the gut microbiota induces an immune response by initiating the gut-brain axis and accounts for epileptogenesis. In addition to the above, it can be added that an imbalance between excitatory (glutamate, dopamine, noradrenaline) and inhibitory (GABA and serotonin) neurotransmitters in the brain centre lies in the development of epilepsy [77].

Intestinal microorganisms secrete neurotransmitters that can also be generated by stimulation of intestinal cells by gut metabolites. There is evidence that the relative abundance of the genera *Coprococcus*, *Ruminococcus* and *Turicibacter* is positively correlated with glutamate and glutamine levels [78], while abundant colonisation of the gut by *A. mucinophilia* and *Parabacteroides* is able to alter amino acid levels in the intestinal lumen, serum and hippocampus in such a way as to balance the amount of seizure-related neurotransmitters, thereby providing a protective anticonvulsant effect [79].

However, the composition and structure of GMB are so complex and poorly understood that it is problematic to identify certain bacteria as the most "beneficial" or "dangerous" in epilepsy [80–82].

The most important neurotransmitter — 5-hydroxytryptamine (5-HT, serotonin) is involved in the regulation of cognitive, behavioural and other mental functions of humans. Its action is realised through 7 main families of serotonin receptors (5-HT1-5-HT7) and at least 14 subtypes, which determines their different response to specific (including pharmacological) ligands.

The main source of serotonin in the intestine is enterochromaffin cells (ECs) [83]. It is presented that patients with temporal lobe epilepsy are deficient in serotonin. However, it has been observed that fluctuations in its concentration in the gut are not able to directly affect the brain because it does not penetrate the blood-brain barrier [84]. However, 5-HT released by ECs may have a potential effect on signal transduction along the brain-gut axis, regulating afferent activity of the abdominal part of the vagus nerve [85] and inflammatory responses [86]. It has been suggested that altered levels of 5-HT in the gut are associated with epilepsy. But there is no evidence to support this.

The concentration of another neurotransmitter, N-acetylaspartic acid (NAA), is possibly decreased in patients with epilepsy. However, a pilot study found that low levels of NAA are associated with faecal *Ruminococcus faecalis* and this process is mediated by serum cortisol [87].

The role of other neurotransmitters in the pathophysiology of epilepsy is known, but it is not carried out by the gut microbiota. It has been observed that norepinephrine has a dual effect on the onset of epilepsy depending on concentration: at low doses it has a proepileptic effect, while high doses can trigger epilepsy [88].

Dopamine and acetylcholine are closely related to epilepsy and are able to indirectly influence brain function through the enteric nervous system, vagus nerve and by regulating the expression of peripheral receptors [89]. For example, acetylcholine (ACh), a major stimulant of the autonomic nervous system, activates signal transduction via cholinergic and nicotinic receptors. Accumulating evidence suggests that dysfunction of nicotinic receptors, which are widely expressed in hippocampal neurons and cortex, may be significantly involved in the pathogenesis of epilepsy. The dopamine-norepinephrine-adrenaline cycle induces hormonal and neuronal pathways. Serotonin, norepinephrine, histamine and melatonin can act as both hormones and neurotransmitters [90, 91].

THE ROLE OF FACTORS CAPABLE OF REMODELLING THE GUT MICROBIOME AND INFLUENCING THE PROGRESSION OF EPILEPSY

There is no doubt that diet, probiotics, antibiotics, and a number of other factors modify GMB composition. Recently, there is emerging work with a good evidence base that these same predictors can affect the nervous system and reduce or increase epileptic seizures.

The ketogenic diet (KD) has been successfully used to compensate for the course of a group of severe neurological diseases [92, 93] and is recommended for children as an alternative treatment for any form of epilepsy when traditionally used antiepileptic drugs are ineffective (the level of persuasiveness of recommendations is A, the level of evidence is 1) [43].

However, fundamental mechanisms of the antiepileptic effect of KD need further investigation. Current explanations are based on the operation

of neurotransmitters, brain energy metabolism, oxidative stress and ion channels [94], and microbiota remodelling [40, 95].

Adherence to classical KD for one month is accompanied by a significant decrease in total SCFAs, predominantly due to acetate, propionate and butyrate. This is due to a drastic restriction of fermentable carbohydrate intake and a decrease in the number of fermenting bacteria [96].

Some SCFAs (propionate and butyrate) have antiepileptic effects because they provide maturation of microglia of the enteric nervous system and brain and reduce the permeability of the blood-brain barrier. Butyrate improves mitochondrial dysfunction and protects brain tissue from oxidative stress and apoptosis via the Keap/Nrf2/HO-1 pathway, thereby increasing seizure threshold and reducing seizure intensity [96]. Propionate treatment can reduce seizure intensity and prolong the latency period of seizures by reducing mitochondrial damage, apoptosis, hippocampal damage and neurological deficits [97].

A 2016 systematic review presented 38 randomised controlled trials (RCTs) investigating the effects of probiotics on CNS function in both animals and humans using a specific probiotic dose and duration of administration. Three strains of bifidobacteria *(B. longum, B. breve, B. infantis)* and two strains of lactobacilli (*L. helveticus, L. rhamnosus*) were tested at doses ranging from 10^8 to 10^{10} CFU. The course of treatment was 2 weeks in animals and 4 weeks in humans. Tested probiotics have shown efficacy in the improvement of behaviour associated with psychiatric disorders such as anxiety, depression, autism spectrum disorder (ASD), obsessive-compulsive disorder, and memory recovery (spatial and non-spatial) [98].

In a prospective study of the efficacy of a probiotic mixture in patients with PRE, it was found that the frequency of seizures decreased in 28.9% of patients by more than 50%. In 76.9% of these patients, the positive effect persisted 4 months after discontinuation of treatment. This study showed that adjuvant probiotics reduce seizure frequency and can be used as an adjunctive treatment to AED [99].

In an experimental model of PTZ-induced epilepsy, a group of mice supplemented with probiotics did not develop complete kindling (epileptogenesis) due to an increase in GABA in brain tissue. Consequently, the inclusion of probiotic in the therapy significantly reduced the occurrence of sustained hyperactivity of neurons due to their profound disinhibition caused by the insufficiency of inhibitory control mechanisms and the activity of exogenous (endogenous) factors (PTZ) that caused excitation and disruption of antagonistic regulation between excitation and inhibition processes [100].

The use of synbiotic or probiotic *Lactobacillus fermentum MSK 408* in combination with KD in the treatment of PTZ-induced seizures reduced the side effects of KD without impairing its antiepileptic effects. Both KD and probiotic were found to increase GABA metabolism by regulating the gut microbiota [61].

It has been observed that saplementation of the diet of PRE patients with synbiotics enriches the GMB with SCFA-producing microorganisms [17], and *Lactobacillus fermentum MSK 408* modulates the GMB, has an effect on SCFA and restores serum lipid profile and mRNA expression of tight contact proteins in both the gut and CNS [24]. These are preliminary observations for additional probiotic effects in the treatment of PRE. It is likely that probiotics can be an adjunctive treatment for refractory epilepsy and used in combination with KD. However, further, larger placebo-controlled, experimental and clinical studies of the mechanism of action of pro- and synbiotics are needed.

Z. He et al. (2017) presented a clinical case of a young man suffering from Crohn's disease and seizures for 17 years. The patient underwent faecal microbiota transplantation for the treatment of Crohn's disease. During 20 months of follow-up, he did not record a single episode of seizures despite discontinuation of sodium valproate [101].

It was shown that treatment of newborns diagnosed rotavirus gastroenteritis with probiotics (*Saccharomyces boulardii* or *Lactobacillus casei*) reduced the risk of seizures 10-fold compared to the control group (children who did not receive probiotics). The authors suggested that *S. boulardii* suppresses paroxysmal brain activity by inhibiting the structural protein NSP4, which activates chloride channels and reactive oxygen species, or by suppressing the inflammatory response in general [102].

Six patients with PRE have been described, five of whom had complete cessation of seizures and one of whom had more than 90% reduction in seizure frequency on antibiotic (AB) treatment. After discontinuation of treatment for a fortnight, seizures recurred in all patients [103]. It is possible that such a positive effect of AB therapy is due to inhibition of the growth of one or more intestinal microorganisms responsible for the production of compounds that destroy the balance between excitation and inhibition: the main factor provoking the development of seizures. However, other mechanisms cannot be excluded.

Some ABs can cause epilepsy. For example, lactam ABs, including penicillin, cephalosporins,

and carbapenems, most commonly induce seizures [104]. IV generation of cephalosporins: imipenem and ciprofloxacin in combination with renal dysfunction, brain damage and epilepsy pose an increased risk of symptomatic seizures.

The use of ABs has short- or long-term effects on GMB composition in both humans and animals [105]. Often, ABs disrupt the balance of gut microorganisms and cause disease. Although there are ABs that increase the abundance of beneficial microorganisms and play a positive role in the structure of the gut microbiota [105].

Different groups of ABs remodelling the GMB in different ways. For example, macrolides inhibit the growth of *Actinobacteria* (mainly *Bifidobacteria)* [106, 107], oral vancomycin decreases the number of *Firmicutes* and increases the number of *Proteobacteria* [108]. Penicillin has a weak effect on human GMB [108]. The extent of amoxicillin-induced epilepsy is independent of the composition of the gut microbiota, which contradicts the hypothesis that GMB acts as a "bridge" in AB-induced epilepsy. It should be considered that the effects of AB on the microbiota are related to the initial composition of the microbiota and the habits of the macroorganism [108, 109]. In the future, a multicentre study is needed to further elucidate the specific effects and mechanisms of action of different antibiotics on epilepsy.

Antibiotics can cause the drug interactions with AEDs, which alters the operability of the last ones and consequently attenuates or enhances seizure susceptibility. Most clinically important interactions between antibiotics and AEDs result from induction or inhibition of cytochrome P450 enzymes that metabolise the drugs. This phenomenon has been widely described for carbamazepine, phenytoin, phenobarbital and rifampicin [110].

Thus, studies of microbial diversity in patients with PRE have captured that this form of the disease is often associated with the prevalence of *Firmicutes* phyla microorganisms. The use of agents (pro-, antibiotics, etc.) capable of converting GMB also converts paroxysmal brain activity in epilepsy. The study of the individual "metabolic profile" in epileptic patients when using pro- and antibiotics may possibly introduce new strategies in the treatment of this disease.

CONCLUSION

The microbiom–gut–brain axis refers to the bidirectional relationship between the gut and brain and regulates gut and CNS homeostasis through neural networks and neuroendocrine, immune and inflammatory pathways. Improvements in sequencing technology have highlighted the regulatory role of the gut microbiota in epilepsy.

Based on these findings, various means aimed at the recovery of a healthy microbial community (the diet, pre-, probiotics, antibiotics and even faecal microbiota transplantation) should be used, which may become in the near future one of the alternative treatments for the refractory epilepsy and improve the quality of life of patients suffering from this disease.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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