DOMAŃSKA, Natalia, BOJARSKA, Małgorzata, BOGUCKA, Julia, BRZYSKA, Anna, KOSOWSKA, Michalina and PIECEWICZ-SZCZĘSNA, Halina. Unveiling the Potential of Gut Microbiota: Promising Approaches to Treat Drug-Resistant Epilepsy. Quality in Sport. 2024;26:55121. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.26.55121
https://apcz.umk.pl/QS/article/view/55121

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 12.09.2024. Revised: 19.09.2024. Accepted: 12.10.2024. Published: 14.10.2024.

Unveiling the Potential of Gut Microbiota: Promising Approaches to Treat Drug-Resistant Epilepsy

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ABSTRACT

Introduction: Epilepsy is a chronic, non-infectious disease of the brain. Data shows that even 70 million people worldwide suffer from it and one-third of them fail to control it with anti-epileptic drugs. The gut microbiota has an impact on the course of the disease. The microbiota

mediates between the gastrointestinal system and the central nervous system. **Purpose**: The aim of the work is to analyse how modification of the gut microbiota affects patients with drug-resistant epilepsy. **Material and method**: In December 2023, an extensive search was conducted and articles found in the Medline (PubMed) databases were selected by using the following keywords: drug-resistant epilepsy, gut microbiota, gut-brain axis, ketogenic diet, probiotics, faecal microbiota transplantation, to focus on recent developments and advancements in the field, the search was limited to articles published between 2017 and 2023. **Conclusions**: The intestinal microbiota in drug-resistant epilepsy (DRE) patients differs from that of healthy individuals or drug-sensitive epilepsy patients. Acknowledging the presence of the gut-brain axis and its impact on the central nervous system, we can view altering the flora as a potential therapeutic approach for DRE patients. The ways in which microbiota changes have been confirmed by research include: ketogenic diet, antibiotics, probiotics and fecal microbiota transplantation (FMT). Modifying the microbiota through these mentioned methods is all promising for treating DRE.

KEY WORDS

drug-resistant epilepsy, gut microbiota, gut-brain axis, ketogenic diet, probiotics, faecal microbiota transplantation

INTRODUCION AND PURPOSE

Epilepsy is a chronic, non-infectious disease of the brain. It is one of the most common neurological conditions. Data shows that from 50 to 70 million people worldwide suffer from it and these are patients of all ages. About 5 million people are diagnosed with epilepsy each year. 70% of patients are able to live without any seizures if the disease is properly diagnosed and treated with individually selected therapy [1]. It is characterised by recurrent seizures, which are the result of excessive electrical discharges in brain cells that are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalised) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function. The causes of epilepsy can be various: structural, genetic, infectious, metabolic, immunological and idiopathic [2,3]. The aim of this review is to highlight the role of the gut microbiota in the treatment of drug-resistant epilepsy. Explain what the gut-brain axis is and present ways to modify the gut microbiota as a promising treatment method and

improve the quality of life of patients with drug-resistant epilepsy. Modifying gut microbiota presents a promising avenue for managing drug-resistant epilepsy (DRE). Approaches such as fecal microbiota transplantation (FMT), ketogenic diet (KD), probiotics, and antibiotics show potential in altering gut microbial composition and improving seizure control.

Material and methods

In December 2023 scientifics, reviews articles and websites were reviewed by using Medeline (PubMed) and Google Scholar. Articles were searched using keywords: drug-resistant epilepsy, gut microbiota, gut-brain axis, ketogenic diet, probiotics, fecal microbiota transplantation. The available articles and web sites were analyzed and 41 were selected for final analysis. The collected knowledge was completed and systematized to achieve the final effect of the review. By synthesizing the information from various sources, the review aimed to provide valuable insights into the role of the gut microbiota in drug-resistant epilepsy and its potential implications for treatment and management.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Drug - resistance epilepsy.

According to research, around a third of adults and a quarter of children are unable to control epilepsy despite there being over 30 antiseizure medications available. The International League Against Epilepsy proposed a definition of resistant epilepsy as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom". There are several therapeutic options for this type of epilepsy, including e.g.: resection surgery (consisting of the surgical removal of the area of the brain generating pathological bioelectric discharges), laser thermotherapy, immunotherapy, deep brain stimulation, vagus nerve stimulation. A method of treating drug-resistant epilepsy that brings satisfactory results is also the use of dietary therapies, for example a ketogenic diet (KD), and modifying gut microbiota [4-6]. Modifying the gut microbiota through diet, antibiotics, probiotics and faecal microbiota transplantation (FMT) is all promising methods for treating drug-resistant epilepsy. Overall, the multifaceted nature of drug-resistant epilepsy necessitates a comprehensive approach to treatment clinicians can offer new avenues of hope for individuals who continue to struggle with seizures despite conventional treatments.

Analysis of the literature

Recent studies have shown that the intestinal microflora and its metabolites play a huge role in maintaining host intestinal homeostasis. With the development of molecular biology, genomics, bioinformatics analysis technologies or high-throughput sequencing, evidence has emerged showing that an imbalance in the gut flora predisposes to the development of many neurological diseases, including epilepsy [7]. The gut microbiota is all the microorganisms that inhabit the intestines, and the microbiome is the total genetic composition of the microbiota. The microbiota consists of approximately 100 trillion microorganisms - including bacteria, fungi, yeast, archaea, protozoa and viruses. The total mass of intestinal microbes has been estimated at 1-2 kg [8]. Bacteria are the most numerous group, with around 100 species distinguishable. This includes two major phylotypes - Firmicutes and Bacteroidetes - and a smaller number of Actinomyces, Fusobacterium, Proteobacteria and Verrucomicrobia [9–12]. The gut microbiota is formed at birth as a result of maternal transmission of infection, and then by exposure to microorganisms from the external environment. It dynamically changes before the age of 3, especially during the period of weaning from the mother's food. During development it undergoes dynamic changes, depending on diet, medications, diseases, infections and other stressors. Infants' intestines are dominated by Bifidobacterium and Lactobacillus bacteria. Healthy adult intestines mainly contain firmicutes and bacteroides [13–15] The main tasks of the intestinal microbiota include: development and maturation of the intestinal immune system, ensuring metabolic homeostasis and resistance to pathogens, participation in carbohydrate metabolism, body defence mechanisms through synthesis of short-chain fatty acids (SCFA), cytokines, hormones and through modulation of signalling in the autonomic nervous system (AUN), influence on central nervous system (CNS) physiology and neurotransmission through the neural network, activation of the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis (which controls stress responses, mood or immune mechanisms), metabolic and immune mechanisms [16,17]. In addition, the gut microbiota has been shown to influence CNS physiology and neurochemistry, affecting behavior, cognitive function, mood, anxiety and depression [18].

Gut-microbiota-brain axis, neuronal pathways, neurotransmitters, blood-brain barrier integrity, immunity in the central nervous system.

The microbiota and its metabolites, in addition to the vagus nerve fibres and sympathetic fibres leading to the brain, are another source of signalling [19]. The gut microbiota and its metabolic products mediate the bidirectional relationship between the gastrointestinal tract and the central nervous system and are called the gut-brain axis. It is believed to have a role in the pathophysiology of neurological and neuropsychiatric conditions, such as depression, anxiety, schizophrenia, autism spectrum disorders, Parkinson's disease, migraine and epilepsy. The gut-brain axis includes: the gut microbiota and its metabolic products, the enteric nervous system, the autonomic nervous system (sympathetic and parasympathetic branches), the neuroendocrine system, the nervous immune system and the central nervous system. The CNS regulates the function and integrity of the gastrointestinal tract through the HPA neuroendocrine axis, inflammatory and immune pathways and the autonomic nervous system. These pathways regulate intestinal barrier permeability, gastrointestinal motility, gastrointestinal secretory activity and the composition of the intestinal microbiome. In turn, the gastrointestinal tract influences brain function and behaviour by promoting synaptogenesis, activating stress responses, synthesising neurotransmitters (gamma-aminobutyric acid (GABA), noradrenaline, dopamine and serotonin), SCFA and the integrity of the blood-brain barrier (BBB). For example, Candida, Escherichia, Enterococcus, and Streptococcus are among the producers of serotonin, Bifidobacterium generates GABA, and members of the Bacillus family can produce dopamine and norepinephrine (NA). In addition, the intestinal microflora possesses enzymes that control the metabolic pathways of tryptophan, which is a precursor to serotonin. Numerous studies have shown that the gut microflora plays an essential role in the development of specific subsets of lymphocytes. Bacterial colonisation of host intestinal epithelial cells induces the expression of serum amyloid A, which stimulates the secretion of interleukin-6 (IL-6) and interleukin-23 by intestinal lamellar dendritic cells and promotes the differentiation of helper T lymphocyte 17 [20–25]. The microbiota can also affect the levels of other neurotransmitters, including gaseous transducers, neuropeptides, histamine, steroids and endocannabinoids. The intestinal microflora can also affect the integrity of the intestinal barrier, which controls the passage of signalling molecules from the intestinal lumen to the lamina propria, which contains immune cells and the terminal ends of enteric nervous system (ENS) neurons, or to the portal circulation [26]. SCFAs are signalling molecules produced exclusively by the intestinal microbiota during the

fermentation of dietary fibre, and are responsible for a number of physiological processes including modulation of 5-hydroxytryptamine synthesis, neuroplasticity or modulation of the immune system by influencing the maturation of microglia from early stages of human development [10,19] . Recent studies show that epilepsy can develop as a result of activation of the neuroimmune system mediated by inflammation in the nervous system and changes in the activity of the gut flora, which activates immune cells such as B cells and T cells and promotes inflammation of the nervous system by regulating the production of cytokines. In addition, the gut microbiota induces inflammation in the nervous system through activation of astrocytes and microglia, and its quantitative changes also cause a decrease in SCFAs, which promote permeability of the blood-brain barrier . Increased permeability of the BBB and the intestine allows peripheral immune cells and gut microbiota components to enter the brain and activate astrocytes and microglia, potentially causing epilepsy [24,27] .

Changes in gut flora - comparison of normal diet vs. keto // flora in non-dieters vs. dieters.

There are studies that demonstrate changes in gut microbiota in patients with drug-resistant epilepsy. One of them involved healthy patients (control group), drug-sensitive epilepsy (DSE) patients and drug-resistant epilepsy (DRE) patients. Patients in the DRE group showed an increased abundance of rare faecal microbiota. In addition, the DRE group showed increased levels of Firmicutes and decreased levels of Bacteroides. (Specifically, selected Firmicutes species with increased levels included Roseburia , Coprococcus , Ruminococcus and Coprobacillus .) A comparison of the DRE and DSE epilepsy groups showed the relative abundance of Methanobrevibacter, Fusobacterium , Neisseria and Akkermansia in the first group. Interestingly, analysis of the gut microbiome profile showed no significant differences between DSE patients and healthy controls. Another study considered 12 children with DRE aged 2-17 years and 11 healthy parents - the children with refractory epilepsy showed greater diversity, while the microbiomes of the healthy parents showed clear clustering, according to the first principal component analysis of taxonomic and functional profiles. In this case, taxonomic analysis revealed a decreased relative abundance of Bacteroidetes and Proteobacteria along with an increased relative abundance of Firmicutes and Actinobacteria in the microbiota of children with drug-resistant epilepsy compared to control parents [20] . It is noteworthy that concentrations of Bifidobacterium and Lactobacillus were increased in patients with four or fewer seizure episodes per year compared to those with more seizure

episodes, predicting that these two strains may have a protective effect on sensitivity to antiepileptic drugs [23]. Knowing the importance of the gut-brain axis and understanding the differences in the composition of the gut microbiota in healthy and epileptic patients, we can influence the modification of the microbiota by various methods. Modifying the gut microbiota through diet, antibiotics, probiotics and faecal microbiota transplantation (FMT) are all promising methods for treating drug-resistant epilepsy. In the following section of the article, we will discuss each of the methods in detail.

Fecal Microbiota Transplantation (FMT).

Fecal microbiota transplantation (FMT) is a medical procedure that involves transferring fecal matter from a healthy donor into the gastrointestinal tract of a recipient. The purpose of FMT is to introduce a healthy balance of gut microbiota to the recipient's digestive system, which can help restore or improve the microbial diversity and function within the gut. Additionally, emerging research suggests potential applications for FMT in other conditions, including some neurological disorders like epilepsy. The case of a 22-year-old female patient with Crohn's disease and epilepsy was the first case report in the literature of successful treatment of epilepsy with FMT fecal microbiota transplantation. The patient was taking antiepileptic drugs but still experienced 2-3 generalised seizures every year if she had forgotten to take the antiepileptic drug. The stool for FMT was obtained from a healthy primary-school girl. After the FMT she stopped taking anti-epileptic drugs and she had 20-months seizure free. A study suggests that a gut microbiome transplant from a healthy individual may offer seizure protection for epilepsy patients, as indicated by a study. [28,29].

Ketogenic Diet (KD).

The Ketogenic Diet (KD) is based on putting the body into a state of ketosis, which means changing the main energy substrate from glucose to ketones (acetoacetate and beta-hydroxybutyrate). This is possible with the right proportions of nutrients. The KD is based on high-fat foods - they account for 90% of the intake, protein is about 6% (to cover the need for building material), and carbohydrates should be kept to a minimum - 4% [30,31]. It is known that the KD also affects the intestinal microflora, which is associated with the anti-epileptic effect of this diet. It is used as a very effective therapy in the treatment of drug-resistant epilepsy. The mechanism of action of the ketogenic diet may be due to changes in the composition of the intestinal microflora. One of the meta-analyses included 16 studies and

a total of 338 patients, both children and adults (mostly patients over 16 years of age) with symptomatic focal and generalised idiopathic epilepsy who have had at least 2 or 3 seizure attacks per month, using one or two antiepileptic drugs. For the period from 3 to 36 months, they received KD and its modifications as a supplement to pharmacological treatment. In these trials, the proportion of patients who showed more than half a reduction in seizures ranged from 20 to 70%, and the proportion of patients who had seizure relief ranged from 7 to 30%. The discontinuation rate ranged from 12.5 to 82% of patients. Side effects were mild wit weight loss and dyslipidemia being the most common. This meta-analysis showed that the use of a ketogenic diet in adults with drug-resistant epilepsy is an effective and promising treatment [32] . Another study included 91 children of various ages with drug-resistant epilepsy. Patients maintained a ketogenic diet for at least 12 months. After this period, 35.2% of patients remained seizure-free and 70.3% of children achieved a seizure frequency reduction of at least 50% [33] . The ketogenic diet's impact on gut microbiota composition underscores its anti-epileptic properties. Studies demonstrate its effectiveness in reducing seizure frequency, particularly in drug-resistant cases, suggesting a mechanistic link between gut microbiota modulation and seizure control.

Prebiotics and probiotics.

Probiotics are vital microorganisms that provide health advantages to their consumers when digested in sufficient quantity. Prebiotics are on-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon [34,35] . In group of 45 adults with drug-resistant epilepsy were treated with a probiotic cocktail of beneficial bacteria and observed that probiotic treatment reduced seizure frequency by 50% or more in 28.9% of patients. This study suggests that additional probiotics in DRE are safe and may reduce seizure frequency and improve quality of life [36] . In a group of 228 newborns, 78 of them were rotavirus-positive and had epileptic seizures. It was observed that administration of probiotics (mainly Saccharomyces boulardii) was associated with a 10-fold reduction in the risk of seizures. It has been shown that Immediate administration of probiotics after birth can reduce rotavirus-induced epileptic seizures in newborns [37] . These findings suggest that probiotics, whether in the form of a probiotic cocktail for adults with drug-resistant epilepsy or specific strains like Saccharomyces boulardii for newborns with rotavirus-induced seizures, may have therapeutic potential in managing epilepsy and reducing seizure frequency. However, further

research and clinical trials are needed to better understand the mechanisms and optimize the use of probiotics in epilepsy management.

Antibiotics.

It is known using the antibiotics can reduct pathological as well as beneficial microorganisms in intestines. The use of antibiotics in patients can lead to dysbiosis of the gut microbiota by modifying its composition by reduction of pathological as well as beneficial microorganisms.The result can be a reduction of pathological microorganisms but also an elimination of beneficial microorganisms [38] . Six patients with drug-resistant epilepsy were observed to be temporarily free of epileptic seizures during treatment with antibiotics. These were drugs belonging to different classes of antibiotics. Five of the six patients them achieved temporary freedom from seizures during treatment; the sixth showed a significant decrease in seizure frequency. Within two weeks of discontinuing treatment, seizures returned with the same frequency as before the implementation of treatment [39] . Based on the results of the study, it was hypothesized that influencing the microbiota through antibiotics led to the observed results. However, it should be remembered that some antibiotics can cause seizures are, for example, beta lactam antibiotics, which include penicillins, cephalosporins and carbapenems, among others [40] Epileptogenesis some types of antibiotics is due to the interference in the GABA-A receptors. The inhibition of GABA led to hyperexcitability of neurons and depolarization of the postsynaptic membrane, lowering the seizure threshold. [41]

SUMMARY

Emerging evidence suggests a crucial link between gut microbiota and neurological conditions, including epilepsy. The dynamic interplay within the gut-brain axis influences neuronal function, immune response, and neurotransmitter production, impacting seizure susceptibility. The intestinal microbiota in drug-resistant epilepsy (DRE) patients differs from the intestinal microbiota of healthy people or even drug-sensitive epilepsy (DSE) patients. Knowing the existence of the gut-brain axis and its influence on the CNS and, therefore, the bioelectrical activity of the brain, we can see the modification of the flora as a therapeutic option for DRE patients. The ways of microbiota changes that have been confirmed by research include: ketogenic diet, antibiotics, probiotics, and faecal microbiota transplantation (FMT). They are all promising methods for treating drug-resistant epilepsy and improving

quality of life by reducing the number of epileptic seizures . Further research is essential to elucidate the intricate mechanisms underlying gut-brain axis dysregulation in epilepsy and refine microbiota-targeted therapies. In conclusion, understanding and modulating the gut microbiota offer innovative strategies for addressing drug-resistant epilepsy. Leveraging the bidirectional communication between the gut and brain holds immense therapeutic potential, paving the way for personalised, microbiota-targeted interventions to improve seizure control and enhance the quality of life for epilepsy patients.

DECLARATIONS

Author contributions

Conceptualization, N.D., M.B., J.B. and H.P-S; Methodology, N.D., A.B and J.B.; Software, N.D., M.K., and M.B.; Check, M.B. and N.D.; Formal Analysis, N.D., M.K. and A.B.; Investigation, J.B., A.B. and M.B.; Resources, A.B., N.D. and M.K.; Data Curation, M.K. and J.B.; Writing – Rough Preparation, M.B., J.B., N.D. and A.B.; Writing-Review & Editing, A.B., M.B. and M.K.; Visualization, H.P-S. and J.B.; Supervision, A.B., J.B. and H.P-S; Project Administration, M.B., N.D., A.B. and H.P-S.
All authors have read and agreed with the published version of the manuscript.

Funding Statement

This research has received no external funding.

Institutional Review Board Statement

Not applicable

Data Availability Statement

Not applicable

Conflicts of interest

The authors declare no conflict of interest.

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