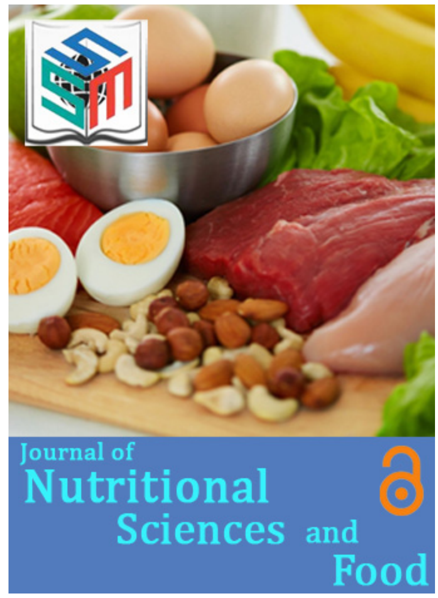

Short Review

Role of Gut Microbiota in Neurological Diseases and Effect of Dietary Factors for Their Management

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Abstract

Human gut microbiota is considered a stand-alone organ responsible for various physiological activities such as immunological signaling *via* the gut-brain axis, energy homeostasis, immune regulation, vitamin synthesis, and digestion. Healthy microbiota has an important role in the protective effect on metabolism whereas dysbiosis may be related to many diseases. This bidirectional communication between human microbiota and health forms the basis of many scientific studies. In recent years, the number of studies on the effects of microbiota or the factors that affect the microbiota on neurological diseases has been increasing. The diet is one of the most crucial environmental factors affecting microbial diversity and neurological development. In this article, we focussed on the bidirectional role of dietary factors (especially vitamins, minerals, and, omega 3 and 6 fatty acids and polyphenols) that have an important role at the gut-brain axis that may be effective on neurological disease development and some of the therapeutic diet approaches on neurological disease and gut microbiota interactions.

Keyword: Diet; Microbiota; Mineral; Neurological Disease; Polyphenols; Vitamin

Introduction

Human gut microbiota is considered a stand-alone organ responsible for various physiological activities, such as immunological signaling *via* the gut-brain axis, energy homeostasis, immune regulation, vitamin synthesis, and digestion [1,2]. It is a reservoir of a diverse range of microbiota alternation in the specific group of intestinal microbiota that causes various diseases.

The intestinal microbiota is principally affected by gender, age, drugs, lifestyle, dietary habits, genetic, and environmental factors [3]. Diet, as the leading factor, affects the composition, diversity, and functionality of the gut microbiota. Especially, dietary components (total energy, carbohydrate, protein, fat, fiber and phytochemicals, vitamins and minerals), dietary patterns (fermented milk products, whole grains, oilseeds, vegetables-fruits, etc.), and nutritional habits (Western-style diet, Mediterranean diet, vegetarian diet, etc.) have an important role on the intestinal environment [4]. In recent years, the importance of the intestinal microbiota on human health is highlighted by the communication between 'bacterial communities' and the rest of the body and especially with the brain [5]. The gut-brain axis functions as an integrative physiological system that combines endocrine, immunological, nutritional, efferent and afferent neuronal signals between the Gastrointestinal (GI) system and the brain. Disturbances or irregularities in the homeostasis of the gut-microbiota-brain axis have been associated with a variety of immunological, neurological, and psychiatric conditions [6]. Figure 1, shows the factors that have an effective role on gut microbiota composition and the bidirectional link between gut-brain-axis.

Different variables such as health, method of birth delivery, heredity, and drugs can influence the makeup of the gut microbiota, but diet is considered one of the most important factors on the human gut microbiota from infancy to old age [7].

On the basis of the nutritional perspective, the scientific literatures mostly focused on the possible effects of probiotics and prebiotics on the gut-brain axis and indirectly on neurological diseases [8]. The vitamins, minerals, and polyphenols are not well recognized or well understood regarding their effects on the gut microbiome and brain axis. This may be due in part to the absorption of most vitamins or minerals in the upper small intestine, or the low concentration absorption ratio (5-10%) of phenolics, this situation resulting in low concentration of vitamins, minerals, or polyphenols reaching distal parts of the gastrointestinal tract [9].

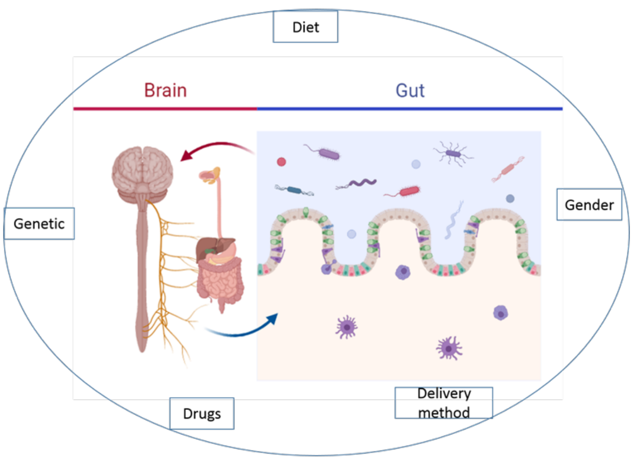

Figure 1: The factors that effects on gut microbiota and bidirectional link between gut-brain axis.

In this article, we focussed on the bidirectional role of dietary factors (especially vitamins, minerals, and polyphenols) that have an important role on the gut-brain axis that can be effective on neurological disease development and some of the therapeutic diet approaches on neurological disease and gut microbiota interactions.

Link between Nutrition and Bacterial Profile of Neuroinflammatory Disorders

The gut microbiota is consist of four major (*Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria)* and two minor phyla (*Verrucomicrobia* and *Fusobacteria*) These commensal bacteria not only communicate with each other but also with host gut epithelium, to maintain the gut homeostasis and improve the host immunity [8].

Different dietary patterns, particularly, the composition of macronutrients and micronutrients of the diet and nutritional sources of macronutrients, contribute to gut microbiota remodeling. Diet induced dysbiosis has mostly been associated with the alternation of gastrointestinal function, immune function and gut bacterial composition and the loss of gut homeostasis, which have been implicated in the pathogenesis of gut brain disorders [10].

Diet has an intense effect on many neuromodulators and neurotransmitters, such as the gut microbiota, enteric nerves enterochromaffin cells, GABA, serotonin, monoamines, and brain-derived neurotrophic factors [11]. The intestinal bacterial profile of some neurological diseases is summarized in table 1.

The main link between nutrition and neuroinflammatory disorders is intestinal dysbiosis caused by poor (especially western

	Amount of specific groups of gut microbuita		
Disorder	**Increased**	**Decreased**	**Reference**
Multiple sclerosis	*Pedobacteria, Flavobacterium, Pseudomonas, Mycoplana, Acinetobacter, Eggerthella, Dorea, Blautia, Streptococcus* and *Akkermansia*	*Prevotella, Bacteroides, Parabacteroides, Haemophilus, Sutterella, Adlercreutzia, Coprobacillus, Lactobacillus, Clostridium, Anaerostipes* and *Faecalibacterium*	Schepici, G., et al. (2019) [12]
	Methanobrevibacter and *Akkermansia muciniphila*	*Prevotella, Faecalibacterium prausnitzii, Bacteroides coprophilus, Bacteroides fragilis*	Mirza, A., et al., (2020) [13]
Epilepsy	*Firmicutes, Proteobacteria, Verrucomicrobia* and *Fusobacteria*	*Bacteroidetes* and *Actinobacteria*	Arulsamy, A., et al., (2020) [14]
Parkinson's Disease	*genera Akkermansia* and *Catabacter*, as well as *families Akkermansiaceae*, were increased,	*Roseburia, Faecalibacterium* and *Lachnospiraceae ND3007 group*	Nishiwaki, H., et al., (2020) [15]
	Lactobacillus, Bifidobacterium, Verrucomicrobiaceae and *Akkermansia*	*Faecalibacterium spp., Coprococcus spp., Blautia spp., Prevotella spp.* and *Prevotellaceae*	Gerhardt, S. (2018) [16]
Autism	*Akkermansia, Bacteroides, Bifidobacterium* and *Parabacteroides*	*Faecalibacterium*	Xu, M., et al., (2019) [17]
Cerebral palsy (Children)	*Bacteroides, Parabacteroides, Clostridium, Faecalibacterium* and *Phascolarctobacterium*	*Coprococcus* and *Bifidobacterium*	Iglesias-Vázquez, L., et al, (2020) [18]

Table 1: Intestinal bacterial profile of some neurological diseases.

diet type) eating habits. Intestinal dysbiosis causes low-grade endotoxemia, disruption of the intestinal barrier, infiltration of LPS, protein and immunologically important cells into the circulation, followed by increased low-grade systemic inflammation, disruption of the BBB, and the activation of microglia and astrocytes, which triggers neuroinflammatory diseases [19].

Role of Some Dietary Factors in Neurological Health Status and Microbiota Interactions

Vitamins

The stability of the lipid in the nerve cell membrane is critical for maintaining synaptic plasticity, preventing the death of nerve cells, and nutrition have a direct effect on the central nervous system and neurotransmitters [20].

The formation and maintenance of nerve cell membranes is a dynamic process that is highly dependent on diet. For example, phosphatidylcholine is an important phospholipid in nerve cell membranes, and its synthesis in the brain requires choline, uridine, and Polyunsaturated Fatty Acids (PUFAs) [such as Docosahexaenoic Acid (DHA)], mainly derived from diets [21]. Dietary composition is also critical for the maintenance of neural structure and function. B group of vitamins (folic acid B6 and B12) play a vital role in both single carbon metabolism and nervous system metabolism. It consists of the bidirectional methionine-homocysteine cycle through these vitamins. When these vitamins are insufficient in the diet, S-Adenosyl Homocysteine (SAH) accumulates in the diet because homocysteine is not methylated [22]. Homocysteine levels were found to be high, and folic acid and B12 levels were found to be low especially in patients with Alzheimer's [23].

Some vitamins are produced by the commensal bacteria in the intestines as well as dietary sources. Especially vitamin B_{12} and vitamin K both are produced and consumed by the microbiota in the intestine. Dietary B vitamins are generally absorbed through the small intestine; bacterial B vitamins are produced and absorbed mainly through the colon [24]. The decrease of these vitamins from diet or the imbalance of bacterial colonization could lead to disruption of the gut-brain system [25].

Vitamin D receptors are found in neurons and glial cells in the nervous system, with the highest expression in the hippocampus, hypothalamus, thalamus, and subcortical gray nuclei and substantia nigra. Vitamin D helps regulate neural differentiation and maturation. It also provides control of the synthesis process of different neuromodulators (e.g. Acetylcholine [Ach], Dopamine [DA] and Gamma-Aminobutyric [GABA]) [26]. Moreover, vitamin D has an important role in the intestinal system. Vitamin D/VDR signaling is critical in intestinal barrier function, innate and adaptive immunity, and homeostasis [27].

As emphasized before, vitamin D has important roles and many receptors in the intestinal and nervous systems. The deficiency of vitamin D can lead to gut-brain axis signaling disruption. Especially in multiple sclerosis patients, Vitamin D levels have been reported to be low [28].

Minerals

Microbiota influence calcium, magnesium, and iron absorption in the intestine. Iron transporters are found in the cecum and right colon, and iron absorption increases in the presence of prebiotics that encourages the growth of bacteria and produces propionate. Luminal minerals, such as calcium, iron, and other micronutrients, have been shown to modulate the microbiome [9].

This mineral's low bioavailability may result in neurologic symptoms of the central and peripheral nervous systems. Calcium, for example, stabilizes excitable membranes in nerve and muscle tissue, whereas magnesium primarily has an important role in intracellular signalization and is necessary for the activation of numerous intracellular enzymes [29].

Omega fatty acids

The central nervous system is highly enriched in long-chain Polyunsaturated Fatty Acid (PUFA) of the omega-6 and omega-3 series. These fatty acids play an active role in the central nervous system either by participating in the membrane structure of neurons or by means of lipid-structured messengers. In addition, omega-3 PUFA may also have significant neuroprotective potential in acute neurological injury [30]. On the other hand, omega-3 fatty acids help maintain the intestinal wall integrity and interact with the host's immune cells, influence the gut-brain axis, acting through gut microbiota composition [31].

Polyphenols

Polyphenols are naturally antioxidants sources of diet especially intake to metabolism by creals, fruit (berries), some seeds (flaxseed) and nuts (chestnut, hazelnut), vegetables, pulses, beverages such as black tea, green tea, and red wine, and dark chocolate [32]. In general, the structure of dietary polyphenols consists of either free (unbound) or bound polyphenols. Because of their remarkable structural diversity, this largely influences their bioavailability. Only 5-10% of the ingested unbound phenolics are absorbed in the small intestine. The unabsorbed molecules are passed down to the colon may accumulate in the large intestine and extensively metabolized by the intestinal microbiota [33]. The formation of bioactive polyphenol-derived metabolites may also benefit the health status of the subjects and this may be through modulation of intestinal barrier function, innate and adaptive immune response, signaling pathways, as well as the ability to modify gut microbiota composition. However, understanding the role of polyphenol on host-microbiota which appropriate polyphenol(s) to be selected is still not clear [34].

Effect of Types of the Diet Plan on the Treatment of Neurological Disorders

In addition to the use of nutritional supplements, various dietary approaches are used in the treatment of some neurological diseases in clinical practice. There are some dietary treatment/preventative approaches for certain neurological diseases.

Ketogenic Diet (KD): A ketogenic Diet (KD) is used in patients with resistant epilepsy to prevent consecutive tremor episodes. The most commonly used diet types are the classic and medium-chain ketogenic diets. In addition to these two diets, a modified ketogenic diet and low glycemic index therapy have also been developed. All these diets are rich in fat (at least 70%) but limited in terms of carbohydrates [35]. Intestinal bacterial profiles and microbial metabolite production vary in epilepsy patients on a ketogenic diet [36].

However, little is known about the mechanisms of action underlying KD. The most widely accepted hypotheses point to the occurrence of metabolic changes in the body, changes in the production of hormones and neurotransmitters, alteration of signalling pathways, epigenetic modifications, and modulation of the microbiota [37-40].

Imbalance in the composition of the gut microbiota is common in individuals with Autism Spectrum Disorder (ASD). Therefore, this imbalance is believed to be important in the frequent occurrence of gastrointestinal symptoms. The integrity of the intestinal barrier and the Blood-Brain Barrier (BBB) is affected in individuals with ASD. Acting as opioid agonists, undigested peptides, toxins, and pro-inflammatory cytokines reach the central nervous system by entering the bloodstream and crossing the BBB. It is assumed that the accumulation of these elements negatively affects brain functions and increases the severity of behaviors specific to autism. It is stated that especially the gluten-free casein-free [GFCF] diet approach reduces toxic peptides and may have beneficial effects on these patients [41].

Mediterranean diet: Mediterranean diet has protective and beneficial effects on neurodegenerative diseases, such as Alzheimer's, Parkinson's, and multiple sclerosis [42]. The classic Mediterranean diet, characterized by high consumption of olive oil, vegetables, fruits, whole grains, legumes, oilseeds, and nuts, includes the consumption of fish and dairy products in moderate amounts, but meat and their products in low and moderate amounts [43]. It is thought that this diet may have a positive effect on health and gut microbiota because it contains high amounts of fiber, mono and polyunsaturated fatty acids, antioxidants, and bioactive compounds [44].

Long-term dietary habits or short-term dietary changes may modulate gut microbiota composition and actively affect the host metabolism. It has been reported that short-term dietary intervention could lead to rapid changes in microbial composition at the species and family level (but not at the phylum) within 24-48 hours [45]. Whether long-term dietary changes cause permanent changes in the gut microbiota is still unknown, mainly due to the lack of long-term human dietary interventions. It is possible that habitual diets have a greater impact on the gut microbiota than acute dietary strategies [46].

Conclusion

Gut microbiota consists of a dynamic microbial system that is constantly changing by many biological variables, including environmental factors.. As a major environmental factor, diet affects the composition, variety, and functionality of the gut-brain axis. Therefore, determining the disease-related intestinal bacterial profiles and determining the effect of nutrition on the intestinal profile and neurological diseases may perhaps be a ray of hope in the prevention, diagnosis, or treatment of neurological diseases.

Conflict of Interest

Authors declare no conflict of interest.

Author's Contribution

Yeliz Serin: concept, writing- original draft preparation, data curation; Aadhya Tiwari: Critical review and editing; Anil K. Verma: Supervision, critical review and editing.

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