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Review

Microbial Influence on Serotonin: A Fascinating Gut-Brain Interaction

Simge Burgaz[1], Oytun Erbaş[1]

ABSTRACT

The second brain, also known as gut microbiota, outnumbers our own cells in our bodies and contains 150 times as many genes as our genome. The impact of gut microbiota on the brain can be estimated by using germ-free animals, fecal transplantation, probiotic supplementation, and antibiotic treatment. An important signaling molecule serotonin (5-hydroxytryptamine; 5-HT) modulates key gut functions such as gut motility, immunity, and gut microbiota composition and function. Despite being dispersed throughout the body, 90-95% of 5-HT is present in the gut. Thus, there is a linkage between gut microbiota and host levels of 5-HT. A wide range of immune-related neurological disorders, neurodegeneration, and emotional dysregulation are affected by alterations in the gut microbiota. This review aims to summarize gut microbiota, its composition, and its effect on 5-HT production.

Keywords: 5-HT, germ-free animals, gut microbiota, second brain, serotonin

Gut microbiota is often referred to as the 'second brain' within our bodies due to its possession of a distinct nervous system that operates independently. The human brain weighs about 1.4 kilograms whereas the gut microbiome weighs about two kilograms. The gut contains a great diversity of bacteria, bacteriophages, viruses, fungi, protozoa, and archaea. These are collectively known as gut microbiota and are responsible for maintaining human health and the pathogenesis of diseases. There are 10^{14} microorganisms in the intestine which is ten times greater than the number of human cells in the human body. This makes up 1-3% of the total body mass. The gut microbiota contains nearly 35.000 bacterial species and the colon has the highest density of the human microbiome.[1] The most abundant organisms are *Firmicutes*, *Bacteroides*, *Proteobacteria,* and *Actinobacteria*.[2,3]

Several studies have shown that the absence of gut microbiota causes abnormal brain development. These findings were obtained using preclinical models such as bacterial injection, probiotic treatment, fecal transplantation, and analysis of germ-free (GF) animals. Germ-free animals that are selectively colonized with one or more species are also known as gnotobiotics and have an important role in addressing the effects of gut microbiota on the brain. These animals' intestinal microbial ecology has been destroyed and raised in a sterile environment. Control groups for GF animals are specific pathogen-free animals that are free from certain pathogens depending on the study subject. Regarding this, compared with the control group, GF animals with the levels of serotonin (also known as 5-hydroxytryptamine; 5-HT), dopamine, and norepinephrine, and their precursor, metabolites, or receptors cause variations across different brain regions. In addition, GF animals showed that recolonization with gut microbiota can reverse neuronal dysfunctions. Every gut is sterile when we are born, but over a lifetime it changes to a different composition of microorganisms, and each gut becomes unique. Several factors such as the way of giving birth (natural or cesarean birth), feeding method (breast or formula milk), host genotype, geographical and cultural factors, intake of drugs, hormone levels, infections, and antibiotic treatment,

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Simge Burgaz. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: simgeburgaz48@gmail.com

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probiotic supplementation and type of diet influence the gut microbiota. Initial microbial community composition is influenced by the delivery method, with the species (such as *Lactobacillus* sp.) of the mother's vaginal and fecal microbiota in infants born vaginally. Infants born via cesarean section have a unique microbiome that is more similar to the skin microbiota (*Staphylococcus*, *Corynebacterium*, *Propionibacterium,* and a low proportion of *Bifidobacterium* spp.) of their mothers.[4-6]

In breastfed infants, there is an increased abundance of *Bifidobacterium* spp. whereas in formula-fed infants there is a low prevalence of *Bifidobacterium* and a higher prevalence of coliforms, *Bacteroides,* and *Clostridium difficile*.[7] Also during pregnancy, alterations in the maternal microbiome caused by the use of antibiotics or probiotics, diet type, immune activation, and stress can modulate the microbiome and neurodevelopment of offspring.[8]

Gut microbiota has a series of roles in the function and development of our brain more than we consider. Microbiota regulate metabolism and the immune system, synthesize vitamins and other nutrients, protect from invaders by building the gut wall, produce antimicrobial chemicals to inhibit pathogens, and produce a series of neurochemicals [gamma-aminobutyric acid (GABA), 5-HT, norepinephrine, dopamine, acetylcholine, and melatonin] that the brain uses for mental and physiological processes. Additionally, it plays a critical role in the maintenance of gastrointestinal tract (GIT) homeostasis. Trillions of bacteria, fungi, and viruses coexist in GIT and reach high densities. Any disruption in the microbial composition and diversity can alter brain function and cause some mental disorders.[5-8]

Gut microbiota synthesizes several compounds and metabolites that affect the brain. Several studies showed that gut microbiota produce metabolites including short-chain fatty acids (SCFAs), indole derivatives, polyamines, organic acids, and vitamins. Mammalian cells cannot synthesize most vitamins, therefore diet is important for vitamin uptake. Some intestinal bacteria can produce vitamin K and several vitamin B. This holds significance as vitamins play roles in both combating bacteria and acting as antioxidants. Additionally, deficiencies in vitamins impact memory, and neurons, and can lead to the development of neurodegenerative conditions.[5,6]

Neurotransmitters are one of these compounds and they can directly interfere with physiological features. Serotonin is isolated from *Streptococcus*, *Escherichia,* and *Enterococcus* species; dopamine is isolated from *Bacillus* species and GABA is isolated from *Lactobacillus* and *Bifidobacterium* species are examples of neurotransmitters in the gut.[9] Most of these compounds cannot cross the blood-brain barrier (BBB), but their precursors which are also produced by microorganisms can cross and increase levels in the brain. For example, tryptophan, a 5-HT precursor, and tyrosine, a dopamine precursor can both cross the BBB and increase levels of 5-HT and dopamine in the brain.[10]

The blood-brain barrier is a selective semi-permeable border of endothelial cells and it prevents harmful compounds from entering the brain and maintains homeostasis of the central nervous system (CNS). The absence of gut microbiota disrupts the permeability and causes damage and neuroinflammation. Microorganisms can regulate CNS processes via the vagus nerve (VN), the hypothalamic-pituitary-adrenal (HPA) axis, tryptophan metabolism, and the ability to synthesize neurotransmitters such as SCFAs. Also, the gut microbiota contributes to gut motor function, which affects the diversity of gut microbiota.[8-10]

COMMUNICATION BETWEEN GUT AND BRAIN

While the gut microbiome affects the brain, the brain affects the gut via neural, endocrine, immune, and humoral links. This bidirectional communication is termed as gut-brain axis (GBA) and it has several roles including monitoring and integrating gut functions, intestinal permeability, neuroendocrine signaling, and linking emotional and cognitive centers of the brain. Stress in our brain decreases the number of beneficial bacteria in the gut, thus making our body vulnerable to infections and causing inflammation. According to several studies, this indicates a feedback effect on behavior. Several studies have found that parental stress, early life stress, and psychological stress all affect the composition and diversity of the gut microbiota. The central nervous system, the enteric nervous system (ENS), the autonomic nervous system, the HPA axis, the immune system, enteroendocrine cells (EECs), the intestinal microbiota and its metabolites are members of the GBA.[11-13]

Essential gastrointestinal functions such as gut motility depend on the ENS. These systems connect the emotional and cognitive centers of the brain with intestinal functions. The enteric nervous system is also known as the second brain and is similar to the

brain structure. According to GF animals, a lack of gut microbiota causes functional abnormalities of the ENS. Enteroendocrine cells influenced by microbial products are responsible for releasing 5-HT that escapes the gut and moves throughout the body. The HPA axis is a part of the limbic system that is involved in memory and emotional responses and coordinates the adaptive responses of the organism to stressors.[14]

By influencing brain neurochemistry, microbiota affects the HPA system. The gut microbiome can influence the expression of brain-derived neurotrophic factor, which is important for memory. Several studies have shown that there is memory dysfunction in GF animals. Communication occurs via central and systemic routes, with the VN serving as the primary central communication route. It is estimated that damaging the VN results in stress responses and behavior changes. This pathway transmits information from the luminal environment to the CNS. On the other hand, the brain uses efferent VG fibers to communicate with the enterochromaffin (EC) cells and EECs. Nonetheless, VN fibers do not make direct contact with the gut microbiota due to their inability to traverse the gastrointestinal barrier. The VN communicates with muscles, regulates heart rate, and connects with the intestine. Gut microbiota receives signals via 100 to 500 million neurons in the ENS.[15]

SEROTONIN

Serotonin has a wide range of effects on brain functions and more by carrying signals between neurons throughout the body as an inhibitory neurotransmitter and hormone. Synthesis of 5-HT is accomplished by neurons in the ENS. Surprisingly, 90-95% of the 5-HT is produced in the gut by EC cells. Enterochromaffin cells also control the secretion of gastric acid. These cells are only about 1% of intestinal cells and are distributed within the digestive tract with distinct properties in different gut segments. As a gut nutrient sensor, EC cells in the lumen can sense the presence of nutrients, bile acids, and metabolites produced by gut microbiota. Several studies showed that glucagon-like peptide 1 (GLP-1) secretion from EECs and activation of its receptors can release 5-HT. The main functions of 5-HT are to control gut motility, mood, cognition, appetite, and sleep. Other than EC cells, particular types of neurons and immune cells can produce 5-HT as well. It can affect the immune system either directly or indirectly and alter the gut microbiota composition. The immune system is important for our body's health to fight against pathogens and commensals. Its control holds significance within the gut microbiota since it is influenced by the levels of 5-HT, which are modulated by the activity of microbes. Tryptophan, as an essential amino acid, must be taken by diet and it contributes to 5-HT synthesis in CNS by crossing the BBB via the amino acid transporter. First, it is converted to 5-hydroxytryptophan by a key enzyme, tryptophan hydroxylase 1 (TPH1). Increased levels of tryptophan influence the CNS distribution and utilization.[16,17]

Studies on GF animals have shown that the serotoninergic system is also modulated by the presence of microbiota. In several studies, GF mice showed decreased levels of 5-HT in the blood and colon, while having an increased rate of 5-HT turnover in the brain.[18] According to certain research, 5-HT suppresses the expression of major histocompatibility complex class II and the antigen-presenting capacity of macrophages. The production of neurotransmitters such as 5-HT by the gut microbiota can influence ENS.[19] The antibiotic treatment causes low levels of 5-HT and TPH1 in the gut and delays colon motility.

Probiotics modulate 5-HT levels in the frontal cortex and reduce depressive symptoms. *Lactococcus lactis* subsp. *cremoris*, *L. lactis* subsp. *lactis*, *L. plantarum*, *S. thermophilus*, *Candida*, *Enterococcus*, *Pseudomonas,* and *Escherichia* produce 5-HT. During the late growth phase of *E. coli* K-12 cultures also produce 5-HT. *Bifidobacterium infantis* increases levels of plasma tryptophan and therefore affects the transmission of 5-HT. Even though the gut microbiota can generate 5-HT, it does not have the ability to directly impact the brain due to the inability of 5-HT to traverse the BBB. Selective serotonin reuptake inhibitors (SSRIs), which are serotonergic medications can affect microorganisms such as gram-positive bacteria. Some studies suggest that treatment of several anxiety-related disorders with SSRIs shows that anxiety is treatable in adulthood. In order to determine the reversibility of microbial effects on 5-HT, broad-range antibiotics were used to create pseudo-germ-free animals. These animals showed that antibiotics cause decreased intestinal motility and low levels of 5-HT in the colon.[20]

SHORT-CHAIN FATTY ACIDS

Serotonin is released by the neuroendocrine secretory protein chromogranin A. This protein is encoded by the Chga gene and its transcription is modulated by SCFAs. Short-chain fatty acids are

saturated, small organic monocarboxylic acids with a chain length of up to six carbon atoms. These molecules provide energy to epithelial cells, stimulate the release of gut hormones, and modulate the functions of neurons, microglia, and astrocytes. Basically, 5-HT is released from EC by SCFAs, and SCFAs are produced as three main products which are butyrate, acetate, and propionate. These products are produced by the gut microbiota via fermentation of dietary indigestible fibers and transported across the BBB via monocarboxylate transporters.[21] Almost 90-95% of SCFAs are absorbed in the gut mucosa by exchanging Cl^- with HCO_3^- ions and transported to the liver through the portal vein. These functions are performed in the brain via two major cellular mechanisms. The first mechanism is to bind and activate free fatty acid receptor 2 (FFAR2) and FFAR3 and the other mechanism is to induce histone deacetylase inhibitory effects. Acetate is produced by a diverse spectrum of bacteria, whereas butyrate and propionate production are substrate-specific. Acetate production can be induced by a high-fat diet and it has some roles in the activation of the parasympathetic nervous system which can result in increased nutrient intake and cause obesity. Butyrate is produced by *Ruminococcus bromii*, *Faecalibacterium prausnitzii*, *Eubacterium rectale,* and *Anaerostipes coli* which belong to *Firmicutes* phylum.[22]

Butyrate has a neuroprotective effect and it can enhance cognition and activate the VN. Propionate is produced via three different biochemical pathways by several bacteria. Species that belong to the Bacteroidetes and Firmicutes phylum produce via the succinate pathway, species belonging to the Lachnospiraceae family produce via the acrylate pathway and *Ruminococcus* and *Roseburia* species produce via the propanediol pathway. The molar ratio of these products in the intestine is about 3:1:1 and is influenced by several factors.[23]

Short-chain fatty acids are used as an energy source by colonocytes and distributed throughout the body. These compounds facilitate the assembly of tight junction proteins, thus increasing the integrity of the intestinal epithelial barrier. Microglia, astrocytes, and neurons recognize SCFAs that cross into the CNS. It has an important role in the GBA via modulation of the BBB or crossing it to influence cells in the CNS. Short-chain fatty acids influence gene expression in different organs from the gut. For example, microglia which are the macrophages of the brain fight against bacterial or viral infections in the brain and their functions can be regulated by SCFAs. As a main product of bacterial metabolism, SCFAs can stimulate the sympathetic nervous system, increase 5-HT release, affect memory, facilitate T cell generation and homeostasis, stimulate the secretion of GLP-1 which regulates neuroinflammation,[24] activate the vagus pathway, facilitate the secretion of hormones and participate in neuropathologies.[25,26] It has protective roles against some diseases such as diabetes, asthma, colorectal cancer, and Parkinson's disease. Although SCFAs mainly have positive effects, high concentrations of them can cause toxic effects on gut microbiota. The importance of SCFA produced by gut microbiota is understood with GF animals that are treated with SCFAs. Lack of SCFAs resulted in neuron loss and weakened the ENS, but treatment with SCFAs restored this loss.

DIET AFFECTS THE GUT MICROBIOTA

From the moment we are born, even the type of food we eat has a very important impact on our gut microbiota and brain functions. The diet that we choose for our lifestyle can influence the diversity of gut microbiota more than we consider. Presently, its significance is heightened due to emerging dietary patterns and the increased prevalence of prebiotic consumption. The quality of life and the structure of the society we live in affect diet. Gut microbiota produces metabolites in response to changes in diet and nutrients and can regulate 5-HT release. There are mainly two types of diet that are opposite to each other: The Western and Mediterranean diet. The Western diet includes high levels of saturated fatty acid, sugar, and animal protein. It causes an increased risk for dementia, type II diabetes, obesity, and depression. Some researchers showed that this type of diet decreases gut microbial diversity, reduces beneficial bacteria, and increases the level of bile-tolerant microorganisms. Furthermore, elevated sugar levels led to a reduction in the abundance of *Lactobacillus*, *Ruminococcaceae*, and *Lachnospiraceae* microorganisms.[27]

The Mediterranean diet is rich in plant-based protein and includes high levels of bread, fruits, vegetables, nuts and seeds, olives, and olive oil; moderate levels of dairy products, white meat, and fish; and low levels of potatoes, red meat, and sweets.[28] This type of diet is more advantageous for *Bifidobacterium* and *Lactobacillus* species.

Other than diet, the most important subject is probiotics and prebiotics as their food source. These molecules work antagonistically with pathogenic bacteria and promote health. Probiotics are beneficial

to human health by improving skin health, enhancing resistance to allergens, supporting the immune system, reducing pathogenic microorganisms, and protecting macromolecules (such as deoxyribonucleic acid) from oxidative damage.[29]

Prebiotics are the food source for probiotic bacteria in the gut microbiota. Galactooligosaccharide, fructooligosaccharide, and polydextrose are prebiotics that increase the level of probiotic bacteria in the gut microbiota. Probiotics such as *Lactobacillus* and *Bifidobacterium* decrease anxiety, promote health, and improve cognition. Therefore, it is effective in treating mood and anxiety disorders.[30]

Probiotics such as *Lactobacillus* sp. keep anxiety under control by increasing the number of receptors for some neurotransmitters. There are studies about feeding GF animals with probiotics. Research indicates that depression can be exacerbated by the administration of antibiotics, as they disrupt beneficial gut microbiota. Conversely, treatments targeting fungi or viruses, which do not harm gut bacteria, do not seem to have a similar impact. Probiotic strains such as *L. rhamnosus, B. infantis,* and formulations of *L. helveticus* and *B. longum* have shown the linkage between the gut microbiota and depression. As a conclusion, different species of probiotics have different mechanisms and impacts on gut microbiota. Also, bacteria with beneficial effects on mental health are termed "psychobiotics". Studies on GF animals are important for understanding the effects of bacteria on the brain. Several studies in this field have shown that colonization of the gut plays a role in the development and maturation of CNS and ENS.[31]

Lack of gut microbiota as in GF animals, appears to cause some problems with learning and socializing. For example, antibiotic treatment alters microbial diversity and thus defects microglia. Enteric glia are important regulators of diverse gut functions. Microglia are immune cells that maintain CNS processes and homeostasis.[32]

In conclusion, the gut microbiota has a close relationship with the brain. Germ-free animals are one of the most widely used methods in this field and provide significant information. Many studies have been conducted on these animals, but perhaps the most important one is to study the effect of 5-HT. The review briefly summarizes the information needed to understand this effect. The functioning of the human body, the working mechanisms of the brain, and the effects of bacteria are highly complex issues. These topics continue to be studied in a much better way with today's technologies. Antibiotics are known to reduce the number and diversity of bacteria, and the use of probiotics and prebiotics after this treatment ensures recolonization. When the gut microbiota is absent due to antibiotic treatment, SCFAs play a role in mitigating neuronal damage. Especially probiotic bacteria species have a positive effect on the gut microbiota and increase the levels of 5-HT. It is interesting how microorganisms communicate with the brain and some studies have found that this occurs via VN. Serotonin is produced by microorganisms in the gut microbiota but unlike some molecules, 5-HT cannot cross the BBB directly. It has been shown that the precursor of 5-HT can cross the BBB and function in many important roles in the gut and the brain. The gut microbiota has been used to investigate many neuronal diseases and the effects of metabolites produced by microorganisms, type of diet, antibiotic and probiotic uptake, and 5-HT on these diseases.

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