Investigating the Effects of Intestinal Microbiota on the Brain and Human Behavior

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ABSTRACT

Intestinal microbiota are microorganisms that live in the human intestine. The intestinal microbiota contains bacteria, archaea, and eukaryotes, however, bacteria are the prevailing population of the intestinal microbiota. A useful relationship between humans and gut microbiota has been reported. There are many microorganisms living in the intestine that regulate the body's physiological functions. In addition to the impact of microbiota on the digestive system, these microorganisms can regulate the brain and central nervous system function. The enteric nervous system is considered the second brain due to its similarity to the central nervous system and its autonomy. According to the reported results of various studies, intestinal microbiota is an influencing factor in changing behavior and mood and even prevents the development of nervous system diseases like autism, Parkinson's, multiple sclerosis, schizophrenia, and Alzheimer's. The gut microbiota regulates the central nervous system function through the enteric nervous system, the stimulation of the immune system and enteroendocrine cells, and the production of metabolites. Excessive use of antibiotics, improper nutrition, anxiety, stress, and depression cause dysbiosis of the intestinal microbiota, which is an important factor in aggravating nervous system diseases.

Key Words: *Microbiota, Microorganisms, Bacteria, Human behavior, Brain*

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INTRODUCTION

Trillions of microbes live in the human gut and form a community that affects the host through collective metabolic activities. Not only the intestine but also the human gastrointestinal tract contains a dynamic population of microbes, most of which are beneficial and some of which are harmful [1-3]. The microbes in the gut, called the gut microbiota, affect energy production, the immune system, normal body function, thinness, obesity, malnutrition, neurological disorders, mood, behavior, diseases (especially intestinal diseases), and cancer are effective in humans. Gut microbiota is a collection of bacteria, archaea, and eukaryotes that mainly interact with and benefit humans [1]. It is reported that more than 10^{14}

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microorganisms reside in the human digestive tract. Microbiota has many benefits for humans and it has even been determined that it plays a role in the prevention of many intestinal and even non-intestinal diseases [1, 4]. Due to the existence of many different receptors for microbes in the intestine, the intestinal microbiota plays a vital role in strengthening the immune system [5, 6].

Recently, with the existence of microbiota, a term called human superorganism emerged, which means a combination of human and microbial cells. Today, it is estimated that the ratio of human cells to microbiota is 1:1 [7, 8]. Human gut microbiota fluctuates under diet, antibiotic use, maternal pregnancy, type of delivery (cesarean and natural), drug use, and many other factors. The coexistence of microbiota and humans starts from the beginning of human life.

Humans are sterile at birth, and a short time after birth, many microbes (mainly from the mother's milk) enter into symbiosis with the baby [9]. The microbiota of babies born naturally is similar to the vaginal microbiota. The microbiota of babies born by cesarean section is like the microbiota of the mother's skin. It has not yet been determined whether the microbiota at birth affects the development of the brain and nervous system or not [9].

The current study aimed to study the impacts of gut microbiota on the brain and human behavior.

Microbiota and nervous system

Gut microbiota is believed to influence the central nervous system through the enteric nervous system. Due to the similarity of the enteric nervous system to the central nervous system based on autonomy, the enteric nervous system is known as the second brain [9]. The most recent remarkable evidence about gut microbiota is the impact of gut microbiota on behavior, mood, and central nervous system in humans [10]. Research in recent years shows the importance of the brain-gut relationship. Gut microbiota has a direct effect on some diseases such as irritable bowel syndrome, anxiety, stress, depression, behavior, and mental-psychological diseases. On the other hand, things like stress and depression can also be important factors in changing the gut microbiota [10, 11].

The brain-gut axis is the connection between the nervous-gut system and the central nervous system in the brain. This communication is two-way and is carried out from the gut microbiota to the brain and from the brain to the gut microbiota. Gut microbiota can improve neurological disorders such as autism, Parkinson's, and Alzheimer's through the brain-gut axis [12]. The gut microbiome can influence emotional behavior by stimulating endocrine and paracrine signals [13].

Microbiota can even influence social and sexual behaviors. *Lactobacillus plantarum* can change social and sexual behavior in Drosophila. This behavior change is due to the production of special pheromones, whose production is stimulated by *Lactobacillus plantarum* [14, 15].

The role of microbiota in neurological diseases

Recent studies show that gut microbiota is an influencing factor in autism and the development of social behavior [16]. The factor that makes the effect of gut microbiota on autism clearer is the presence of digestive disorders in these patients [17]. In autism, *Lactobacillus* species increase, and *Prevorella* and *Bifidobacterium* species decrease. In depression, Enterobacteriaceae and *Alistpes* increase, and *Ruminococcus* and *Faecalibacterium* decrease. *Lactobacillus* counts are low in stressed individuals. A study on rats has shown that treatment with *Blautia coccoides* alone reduces anxiety levels [16].

Gut microbiota can play a role in improving multiple sclerosis by influencing the immune system. Gut microbiota isolated from patients with multiple sclerosis can improve autoimmune diseases such as autoimmune encephalomyelitis in mice [17]. Research shows that the microbiota of people with multiple sclerosis is different compared to healthy people. Patients with multiple sclerosis have lower numbers of *Butyricimonas*, *Lactobacillus*, *Parabacteroides*, *Parabacteroides distasonis*, and *Actinobacteria* are more common than healthy people. Interestingly, the number of *Methanobrevibacter*, *Akkermansia muciniphila*, and *Acinetobacter calcoaceticus* are more common in patients with multiple sclerosis than in healthy people [18, 19]. *Methanobrevibacter* is a methane-producing archaea that is more common in people with constipation and irritable bowel syndrome. The opinion of most researchers is that maybe the gut microbiota has the potential to treat or prevent multiple sclerosis [19]. Intestinal microbiota is involved in the process of making the myelin sheath in the prefrontal cortex **(Figure 1)**. The prefrontal cortex is involved in attention, memory, learning, emotions, and feelings [20].

One of the most important roles of intestinal microbiota is to prevent a leaky gut. This phenomenon causes thinning and inflammation of the intestinal wall by causing stress and even depression. As a result, pathogenic microbes can directly stimulate the intestinal nervous system and mucosal immunity. This action causes a strong immune response and the production of pro-inflammatory mediators, and finally these mediators are transferred to the central nervous system [21]. The treatment of leaky gut by *Lactobacillus farciminis*, which also reduces stress, supports the above hypothesis. One of the cases proving the connection between gut and brain microbiota, stress, and depression is the reduction of Bacteroidetes in the feces of patients with depression [22].

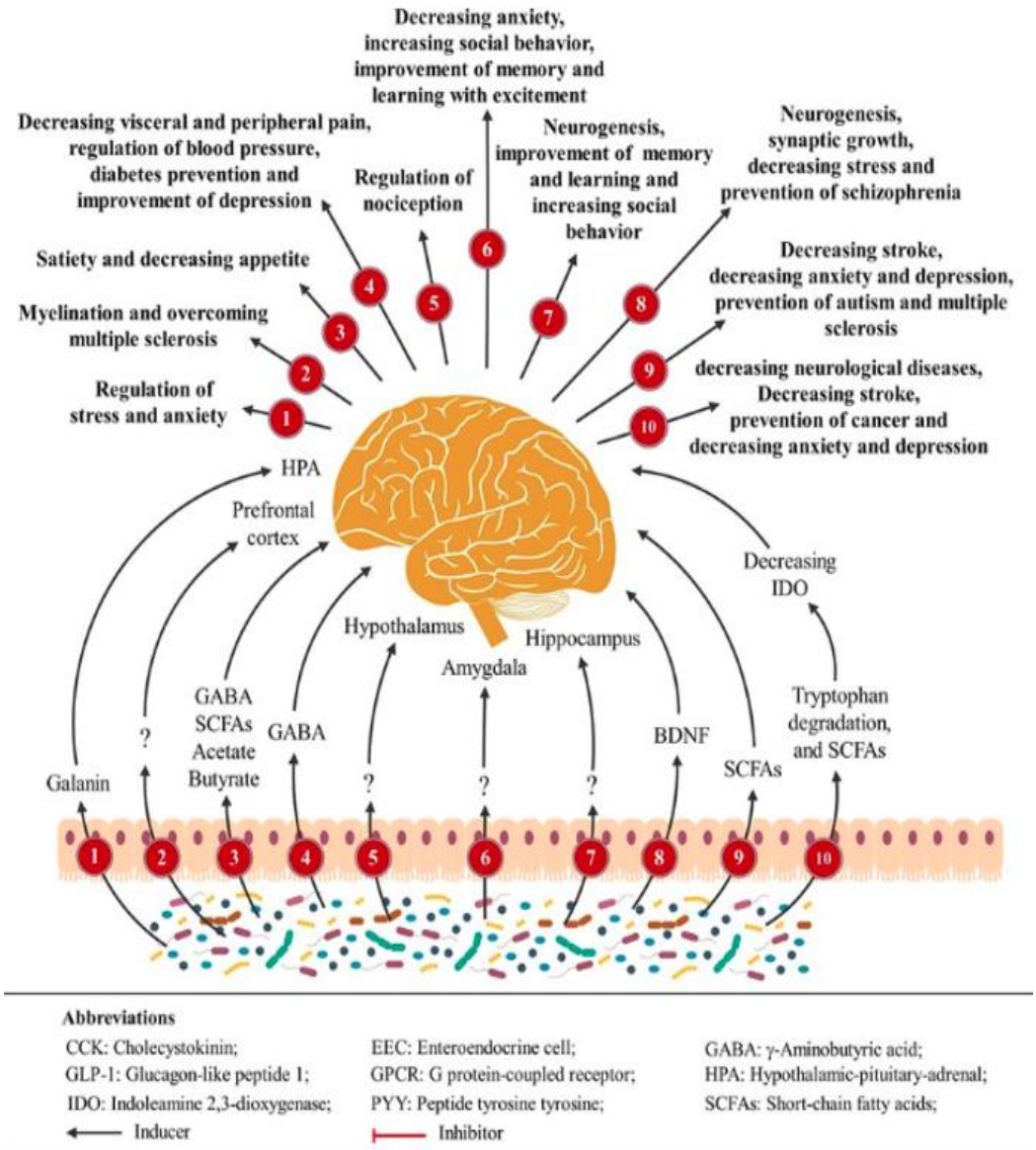

Figure 1. Mechanisms of influence of gut microbiota on behavior and brain.

The relationship between microbiota and anxiety and depression

Mice that receive *Lactobacillus rhamnosus* microbiota over 28 days show less anxiety-like behaviors. Also, rats that used probiotic nutrition *Lactobacillus helveticus* and *Bifidobacterium longum* in 30 days showed a decrease in anxiety in the electric shock model. The findings show that treatment with *Bifidiobacterium infantis* reduces depression. This depression reduction is similar to treatment with citalopram [23].

Animal models have been used in most studies to understand the microbiota role in brain function. Consumption of milk containing *Bifidobacterium animalis*, *Lactobacillus bulgaricus*, *Streptococcus thermophiles*, and *Lactococcus lactis* in humans can affect the brain's response to emotional stimuli. With functional magnetic resonance imaging, it was found that the consumption of probiotic milk for 4 weeks may affect the processing of behavior and emotions in the human brain [24]. Areas such as primary interoceptive and somatosensory are less active in people who consume probiotics.

These areas are activated under the influence of emotional stimulation. A study on 55 people who were prescribed *Lactobacillus helveticus* and *Bifidobacterium longum* showed that this diet leads to a reduction in anxiety and even urinary cortisol. These studies show the impact of gut microbiota on the human brain, behavior, and mood [25].

Microbiota and obesity

Gut microbiota is an effective factor in obesity control by the nervous system. A study on mice with a special diet for weight gain shows that the number of Lactobacillus species decreases with mice obesity [26]. Gut microbiota is directly related to the feeling of satiety. Intestinal microbiota ferments complex carbohydrates into short-chain fatty acids, causing a feeling of satiety. Short-chain fatty acids decrease appetite by changing the levels of

glutamine, glutamate, γ-aminobutyric acid, and neuropeptides **(Figure 1)**. Acetate produced by intestinal microbiota causes physiological and regulatory changes in the hypothalamus and appetite suppression [27]. Intestinal microbiota produces intestinal hormones such as Peptide YY and Glucagon-like peptide 1 by fermenting food to acetate, propionate, and intestinal butyrate. Peptide YY and Glucagon-like peptide 1 affect the hypothalamus and cause a feeling of satiety [28].

Microbiota and neurotransmitters

Gut microbiota increases the level of oxytocin. Oxytocin increases social behaviors, emotions, and feelings and reduces anxiety and stress. It has been found that rats with intestinal microbiota composed of *Actinobacteria*, *Firmicutes*, and *Bacteroidetes* suffer from depression due to low levels of oxytocin [26]. Probably, *Lactobacillus johnsonii* also increases oxytocin and strengthens and improves social behavior and neurological diseases [26]. Gut microbiota regulates oxytocin-expressing cells in the paraventricular nucleus of the brain. *Lactobacillus reuteri* leads to an increase in the number of oxytocin-positive (oxytocin-producing) cells in the paraventricular nucleus. The molecular mechanism of the effect of intestinal microbiota on oxytocin production has not been determined [29].

Intestinal microbiota can control the secretion of hormones and influence the activity of immune cells through the hypothalamic-pituitary-adrenal axis during stress. Corticosteroid hormones released by hypothalamic-pituitary-adrenal axis activity can also regulate intestinal microbiota [30]. Colonization of *Bifidobacterium infantis* in the gut ameliorates behavioral and stress-related brain deficits. Some of the effects of microbiota in the brain take place through the hypothalamic-pituitary-adrenal axis, which can change the host's behavior [31].

Gut microbiota can produce intestinal hormones or peptides like galanin, gastrin, orexin, ghrelin, and leptin. For example, galanin from the hypothalamic-pituitary-adrenal axis regulates the stress response **(Figure 1)**. In addition, leptin also has antidepressant effects [25]. Neuropeptide Y is present in the brain and gut and plays a role in regulating stress, depression, mood, and bowel movement. The myenteric plexus nerve is one of the neural pathways through which intestinal microbiota affects the brain and digestive tract function [32].

Recently, it has been found that the gut microbiota can contribute to the integrity of the blood-brain barrier. This affects the permeability and passage of many substances in the blood through the blood-brain barrier [33]. Tryptophan produced by the intestinal microbiota can pass through the blood-brain barrier [23].

GABA is one of the most important neurotransmitters produced by bacteria. GABA is the main neurotransmitter inhibitor in the human brain [34]. Apart from regulating pain neurons, this substance also plays a role in regulating blood pressure, heart rate, anxiety, and depression [32]. GABA produced by gut microbiota does not cross the blood-brain barrier but is suggested to affect brain function. GABA is produced by the enzyme glutamate decarboxylase. *Lactobacillus brevis* has the necessary capacity to produce GABA and can cause brain health and even partial treatment of diseases such as diabetes [34].

Clostridium sporogenes and *Ruminococcus gnavius* can produce tryptamine through decarboxylation of tryptophan. Tryptamine is produced in the brain and gut, which can affect mood and appetite. Enteric tryptamine can also stimulate the gut to produce serotonin [35]. Unlike enteric serotonin, tryptamine can cross the blood-brain barrier. *Escherichia coli* in the intestine produces norepinephrine, serotonin, and dopamine, and *Streptococcus* and *Enterococcus* bacteria produce serotonin. By producing hormones, these bacteria regulate many functions of the nervous system in the brain [36]. An increase in norepinephrine causes anxiety and stress, but the presence of this hormone improves depression and increases alertness, learning, and concentration [36, 37]. Gut microbiota can regulate the release of norepinephrine and other hormones in the nervous system [36, 37].

Microbiota and learning and memory

Gut microbiota can even be an effective factor in learning and memory. Probiotic feeding enhances object recognition memory in germ-free mice. Object recognition memory is significantly reduced in specific pathogen-free mice treated with antibiotics. Studies show that the intestinal microbiota also affects the spatial memory of mice. In rats that are treated with ampicillin, their spatial memory is disturbed. Rats treated with ampicillin or phencyclidine show poor performance in object recognition memory tests. Antibiotics with microbial dysbiosis (disturbing the balance of intestinal microbes) disrupt object recognition memory and spatial memory. It is expected that the intestinal microbiota in humans is also effective in memory and learning [38].

Effects of antibiotics on microbiota and behavior

One of the ways to regulate gut microbiota and brain function is to use antibiotics. Antibiotics cause many changes in the intestinal microbiota, but the regulation of the microbiota must be precise and controlled. The use of antibiotics to regulate intestinal microbiota increases Firmicutes and Actinobacteria and decreases γ-Proteobacteria and Bacteroidetes. Rifaximin increases Lactobacillus species such as *Lactobacillus casei* [16]. On the other hand, antibiotics and antimicrobial substances cause dysbiosis of intestinal microbiota, change behavior, and increase anxiety and stress. The simultaneous use of

bacitracin, neomycin, and pimaricin after 7 days changes anxiety behavior in mice. After 14 days without antibiotics, these behaviors return to normal [39].

Overall, all the evidence shows that the disturbance in the balance of gut microbiota causes brain and behavior dysfunction. Although antibiotics can be used to regulate the intestinal microbiota, antibiotics are an important factor in disrupting the balance of the intestinal microbiota. If the change in brain function and behavior is attributed to the penetration of antibiotics into the brain, studies show that antibiotics that do not enter the brain also cause changes in brain function and behavior. Antibiotics bacitracin, ampicillin, neomycin, meropenem, and vancomycin disrupt the balance of intestinal microbiota and then cause memory disorders, cognitive disorders, and memory in mice. Antibiotics can change about 30 gut microbiota. The microbiota may return to its original state over time, but it usually does not recover completely. Antibiotics hurt protein activity gene expression and intestinal microbiota metabolism [40]. Today, excessive use of antibiotics is a global challenge and not only causes bacterial antibiotic resistance but may also affect brain function and human behavior and mood [40, 41].

Communication between microbiota and brain through Vagus nerve

Another neural way is the communication of microbiota with the CNS through the Vagus nerve. The Vagus nerve is the main parasympathetic nerve that plays a role in heart rate regulation, intestinal movement, swallowing, food digestion, and bronchial contraction [42]. The vagus nerve is the main nerve of the parasympathetic system and plays a vital role in the impact of gut microbiota on the functioning of the nervous system. The vagus nerve transmits information from the gut to the brain through the ganglion nodes and vice versa. Gut microbiota by producing short-chain fatty acids and stimulating enteroendocrine cells 28 to produce peptides such as peptide YY hormones, glucagon-like peptides, and cholecystokinin changes brain function and behavior by the Vagus nerve **(Figure 2)**. Short-chain fatty acids produced by intestinal microbiota interact with G protein-coupled receptors located on enteroendocrine cells **(Figure 2)** [43].

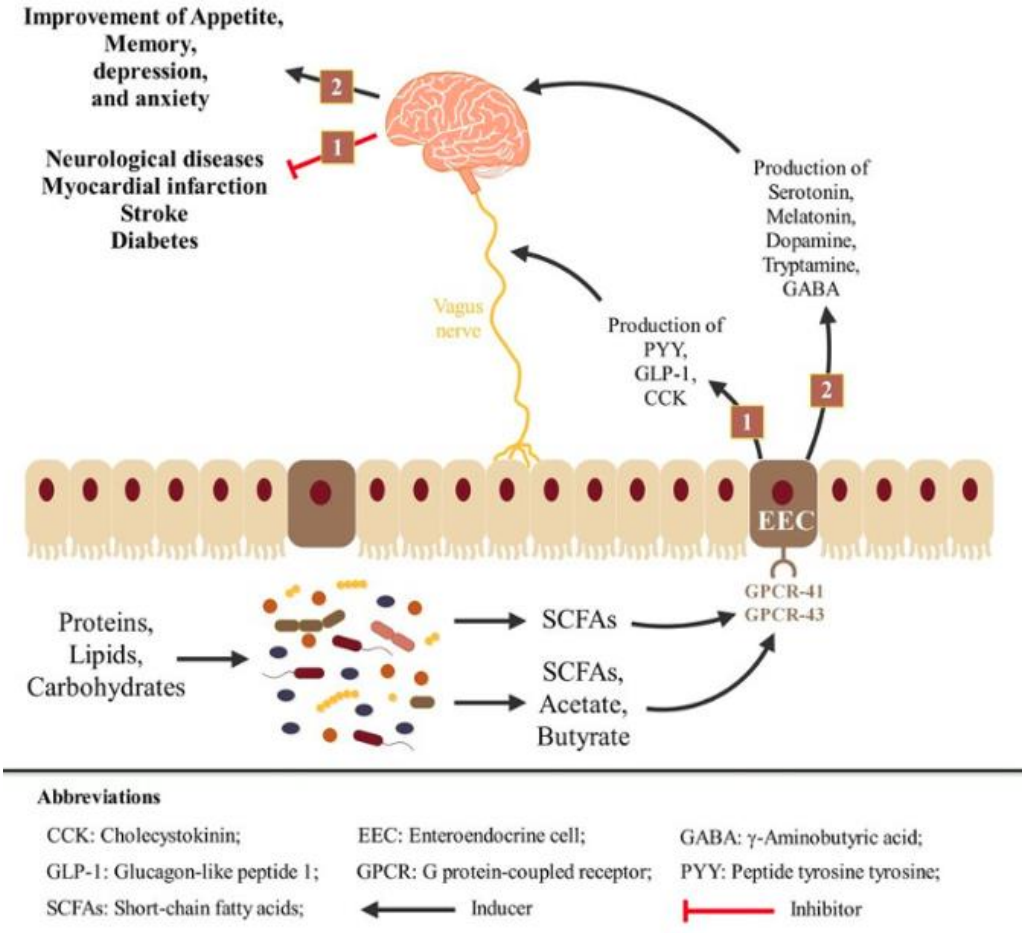

Figure 2. Regulation of brain function by the gut microbiota through enteroendocrine cells and the Vagus nerve.

The relationship between microbiota and the immune system in the brain

The immune system plays a vital role in balancing the brain and gut. Gut microbiota regulates the activity of the mucosal immune system and the extra-gastrointestinal immune system. The digestive tract has immune cells such as Regulatory T cells and antigen-presenting cells that can move from Gut-associated lymphoid tissues to other areas including the central nervous system. Gut microbiota can affect Toll-like receptors and cytokine production. Apart from physiological effects, cytokines can influence behavior and mood [44].

The immune system of mice without microorganisms has almost no activity, but by receiving specific microbiota, their immune system is activated. Filamentous bacteria in the intestine can completely restore the functions of B and T lymphocytes. Intestinal microbiota can be one of the factors related to many neurological and autoimmune diseases such as Alzheimer's, multiple sclerosis, depression, anxiety, autism, and Parkinson's [45]. Microbiota affects the function of microglia. Microglia are the main immune cells residing in the brain. The functions of microglia include phagocytosis, cytokine production, antigen presentation, and inflammatory response activation. Intestinal *Bacteroides distasonis* and *Lactobacillus salivarius* affect mouse microglia. Short-chain fatty acids such as butyrate and acetate propionate can indirectly affect the microglia function. Many neurological disorders, including autism, multiple sclerosis, Parkinson's, anxiety, and even stroke, are related to the intestinal microbiota and microglia activity [46].

Figure 3 shows the pathways involved in bidirectional communication between the brain and gut microbiota.

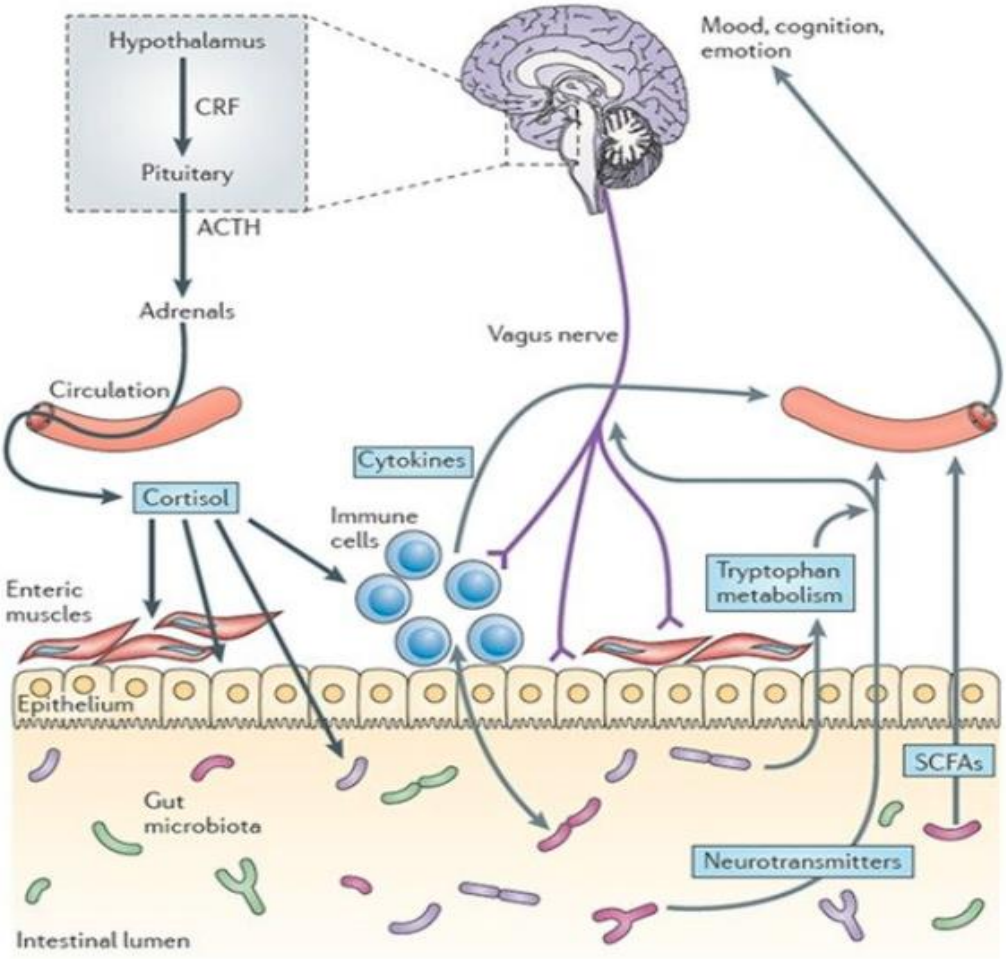

Figure 3. The pathways involved in bidirectional communication between the brain and gut microbiota.

CONCLUSION

The connection between the brain and the gut is a two-way communication. Just as the brain regulates gut function, gut microbiota can also influence brain function. Gut microbiota regulates many human actions and behaviors by producing various metabolites and stimulating the production of different hormones, thus affecting the amygdala, hypothalamus, and hippocampus. Tryptophan produced by gut microbiota plays a vital role in the production of serotonin and ultimately, improving social behavior, anxiety, depression, and stress. Tryptophan also

plays a significant role in obesity by regulating the feeling of satiety. Dysbiosis of microbiota (caused by excessive use of antibiotics and mental illnesses) can be an important factor in changing brain function and human behavior. Gut microbiota through its metabolites and the immune system (by suppressing the production of IL-4, and IL-6-4 and stimulating the production of IL-10), has a regulatory role in brain function and behavior.

It seems that the gut microbiota has the potential to treat many diseases of the nervous system. Taking probiotics designed for neurological patients and proper nutrition is important to prevent and treat neurological diseases. It is hoped that the gut microbiota alone can be effective in the treatment of diseases such as schizophrenia, multiple sclerosis, autism, Parkinson's, Alzheimer's, hypertension, diabetes, and even stroke prevention.

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