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Investigating the pivotal role of gut microbiota in cognitive disorders

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ABSTRACT

Background: The human intestine harbors a collection of microorganisms known as intestinal microbiota, which encompasses bacteria, archaea, and eukaryotes. However, bacteria reign supreme as the most prevalent members of the intestinal microbiota. Notably, the gut microbiota plays a crucial role in regulating various physiological functions of the human body. In addition to its influence on digestion, the gut microbiota also exerts control over the function of the brain and central nervous system, earning the enteric nervous system the title of the "second brain." The behavior and mood, as well as the progression of nervous system diseases like multiple sclerosis, autism, Alzheimer's, schizophrenia, and Parkinson's, can potentially be regulated by the intestinal microbiota. Through the intestinal nervous system, production of metabolites, stimulation of entero-endocrine cells, and the immune system, the gut microbiota plays a role in regulating the function of the central nervous system. Disturbances caused by improper nutrition, indiscriminate use of antibiotics, stress, anxiety, and depression are significant factors that can worsen these diseases and disrupt the balance of gut microbiota.

Kewwors: Cognitive disorders, microbiota, microbiota-gut-brain axis

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1. Introduction

Cognitive disorders encompass a range of brain abnormalities that impact cognitive abilities such as learning, memory, comprehension, and problem-solving. These impairments can be either temporary or progressive in nature. While delirium is fleeting and temporary, dementia typically progresses and becomes severe over time (1). Dementia serves as a broad term for cognitive impairment and is further categorized into subtypes like Alzheimer's dementia, vascular dementia, Lewy body dementia, and subcortical dementia. Additionally, it can also be secondary to other conditions like trauma and Huntington's disease (2). These conditions impose a significant burden on patients and society, affecting their physical, mental, social, and economic aspects. It is projected that the number of individuals with dementia worldwide will exceed 150 million by 2050 (3).

Despite ongoing research, there is currently no definitive treatment for cognitive disorders. Therefore, it is crucial to focus on strategies that can halt or delay the progression of this disease in terms of public health. Recent studies have explored the role of gastrointestinal microbiota in cognitive disorders (4-6). The intestinal microbiota consists of bacteria, archaea, and eukaryotes that have established a mutually beneficial relationship with humans (7). Furthermore, research has demonstrated that the gut microbiota exerts significant control over various aspects of physiology, including brain-gut communication, brain function, behavior (8), neurological disorders, mood, energy production, normal bodily functions, immune system, obesity, thinness, malnutrition, intestinal diseases, and cancer (7).

2. Microbiota and the nervous system

The gut-brain-intestine-microbiota axis is a pathway that illustrates the connection between the gut microbiota, the gut, and the central nervous system (Figure 1) (9). It is believed that the gut microbiota influences the central nervous system through the enteric nervous system (10). The human digestive system is extensively innervated and contains approximately 200 to 600 million autonomic sensory neurons, such as the vagus nerve, which transmit messages to the brain stem and spinal cord. These neurons innervate all parts of the digestive system, and in the intestine, they can be specifically influenced by different bacterial species. For instance, Lactobacillus helvetucus R0052 affects the activity of cells in the hippocampus and amygdala, which are regions of the central nervous system, while Lactococcus lactis subsp cremoris H61 modulates the activity of auditory brainstem neurons. This is why the enteric nervous system is often referred to as "The second brain" (11).

The gut microbiota has a direct impact on certain diseases such as irritable bowel syndrome (IBM), anxiety, stress, depression, and mental-psychological disorders. Conversely, stress and depression can also be significant factors influencing the composition of the intestinal microbiota (12,13). The brain-gut axis is a bidirectional pathway that operates from the brain to the gut and vice versa. Through the brain-gut axis, the gut microbiota can potentially improve neurological disorders such as autism, Parkinson's disease, and Alzheimer's disease (14). Additionally, the gut microbiome can influence emotional behaviors by stimulating endocrine and paracrine signals (15).

3. Microbiota and neurotransmitters

It has been extensively documented that the presence of intestinal microbiota has a significant impact on oxytocin levels in the brain. This is achieved by increasing the number of cells that express oxytocin in the paraventricular nucleus, leading to enhanced social behaviors, emotions, and feelings, as well as a reduction in stress and anxiety (17). Studies have shown that mice with intestinal microbiota consisting of Actinobacteria, Firmicutes, and Bacteroidetes experience depression due to low levels of oxytocin (18). Additionally, there is evidence suggesting that Lactobacillus johnsonii may also contribute to increased oxytocin levels, thereby improving social behaviors and neurological diseases (19). In the absence of gut microbiota, mice exhibit higher concentrations of corticosterone and reduced levels of BDNF. Interestingly, upon the establishment of microbiota in adulthood, these hormone and protein levels partially return to normal, indicating the crucial role of microbiota signals in brain development and evolution (20).

Furthermore, gut microbiota has been found to induce the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus. BDNF is a vital growth factor for the central nervous system, playing a crucial role in its development and adaptability (21). It has been shown to have positive effects on conditions such as depression, schizophrenia, addiction, and various neurological diseases (22). Stress and anxiety in rats have been observed to alter the composition of intestinal microbiota and decrease the production of neurogenesis factors derived from the brain (23).

The intestinal microbiota also has the ability to regulate hormone release through the hypothalamus-pituitary-adrenal axis, which is involved in the body's response to stress. Additionally, corticosteroid hormones released by the hypothalamus-pituitary-adrenal axis can influence the composition of the intestinal microbiota (24). The colonization of Bifidobacterium infantis in the gut has been shown to improve behavioral and stress-related brain deficits. Some of the effects of microbiota on the brain occur through the hypothalamus-pituitary-adrenal axis, which can modulate the host's behavior (25).

Intestinal microbiota has the ability to generate various intestinal hormones or peptides, including orexin, galanin, ghrelin, gastrin, and leptin. One notable example is galanin, which plays a role in regulating the response to stress through the hypothalamus-pituitary-adrenal axis. Additionally, leptin has been found to possess antidepressant properties (26). Another important player in stress regulation, depression, mood, and gut motility is neuropeptide Y (27). Notably, Escherichia coli produces norepinephrine and serotonin, while Enterococcus and Streptococcus produce serotonin, and Bacillus produces norepinephrine and dopamine. These substances have the ability to modulate various functions of the nervous system in the brain (28,29). An increase in norepinephrine levels can lead to anxiety and stress, but it also improves depression and enhances alertness, learning, and concentration (29,30).

4. The relationship between the brain and microbiota

The vagus nerve is widely recognized as a significant neural pathway that connects the microbiota to the central nervous system (31). Through the ganglion nodes, the vagus nerve transmits information from the intestines to the brain. The gut microbiota has the ability to generate short-chain fatty acids and activate enteroendocrine cells, leading to the production of various peptides including peptide YY hormones, glucagon-like peptides, and cholecystokinin. These substances have the potential to impact brain function and behavior by means of the vagus nerve (figure 2) (32).

5. Microbiota and learning and memory

The role of gut microbiota in learning and memory has been widely recognized. Research has demonstrated that probiotic feeding can enhance object recognition memory in rats that are free of gram-negative bacteria. Conversely, object recognition memory is significantly impaired in rats that have been treated with antibiotics and are free of specific pathogens. Furthermore, studies have indicated that the intestinal microbiota also affects the spatial memory of rats. Rats treated with ampicillin or phencyclidine exhibit poor performance in object recognition memory tests. Antibiotics that disrupt the balance of intestinal microbes lead to microbial dysbiosis, which in turn disturbs both object recognition memory and spatial memory. It is reasonable to assume that the intestinal microbiota also plays a role in memory and learning in humans. Probiotic treatments containing Bifidobacterium breve, Bifidobacterium longum, and Lactobacillus fermentum have been found to strengthen object recognition memory. Although the exact mechanism is not yet clear, it has been observed that gut microbiota affects the amygdala in the brain. This impact on the amygdala results in changes in emotions, as well as an increase in memory and learning, along with alterations in excitement, social behaviors, and anxiety. The amygdala, as part of the brain's limbic system, plays a significant role in learning, particularly in relation to excitement, emotional understanding, and responses to pain, happiness, and fear. Additionally, the gut microbiota can influence learning and memory by affecting the brain's hippocampus and hippocampal neurogenesis. Studies have shown that the gut microbiota can also influence the expression of various mRNA and miRNAs in the hippocampus.

6. Microbiota and neurological diseases

Recent research indicates that the gut microbiota plays a significant role in autism and the formation of social behavior (38). The presence of digestive disorders in individuals with autism further supports the impact of gut microbiota on this condition (39). In autism, there is an increase in Lactobacillus species, while Provetella and *Bifidobacterium* species decrease. Conversely, depression is associated with reduced levels of *Enterobacteriaceae* and *ruminococcus*. Stressed individuals tend to have low counts of Lactobacillus, but studies have demonstrated that treatment with *Blautia coccoid* alone can effectively alleviate anxiety levels (40).

7. Microbiota and anxiety and depression

Rats administered with *Lactobacillus rhamnosus* microbiota for a duration of 28 days exhibited a decrease in anxious behavior. Additionally, the administration of probiotic nutrition consisting of *Lactobacillus helveticus* and *Bifidobacterium longum* over a period of 30 days resulted in a reduction in anxiety levels in rats subjected to an electric shock model. Furthermore, it has been demonstrated that *Bifidobacterium infantis* can alleviate depression in humans, with a similar effect to that of citalopram treatment (41).

The consumption of milk containing *Bifidobacterium animalis*, *Lactobacillus bulgaricus*, *Streptococcus thermophiles*, and *Lactococcus lactis* in humans has been found to influence the brain's response to emotional stimuli. Functional magnetic resonance imaging (fMRI) studies have revealed that the consumption of probiotic milk for a duration of 4 weeks may impact the processing of behavior and emotions in the human brain (42). Notably, individuals who consume probiotics exhibit reduced activity in the primary interceptive and somatosensory areas, which are typically activated in response to emotional stimulation (43). A study involving 55 individuals prescribed with Lactobacillus helveticus and *Bifidobacterium longum* demonstrated that this dietary intervention led to a decrease in anxiety levels and even urinary cortisol levels. These findings collectively highlight the influence of gut microbiota on the human brain, behavior, and mood (44).

8. Microbiota and nociception

The available evidence indicates that the nociception experienced in various chronic diseases is influenced by the impact of the intestinal microbiota on the hypothalamus. Nociception, which refers to the perception of pain, triggers a response to harmful stimuli and physical stress. The initial investigation into the role of microbiota in pain regulation was conducted through a colorectal stress test, which is a validated method for assessing colon tenderness and pain (45). This test involves examining the effects of drugs, pressure, genetics, as well as physical and psychological stress on the inflation of a balloon inside the intestine and measuring colon pressure (46).

It has been established that the administration of antibiotics, along with a lactobacillus suspension, during the colorectal stress test reduces sensitivity and pain in the colon of rats. Furthermore, the gut microbiota has the ability to regulate cardiac pain. In addition to its role in regulating visceral pain, the intestinal microbiota can also influence peripheral pain through the immune system. The presence of GABA-producing *Bifidobacterium* has been found to have an analgesic effect. GABA acts as a negative regulator of nociceptive neurons (45).

9. Microbiota and multiple sclerosis

The influence of gut microbiota on multiple sclerosis (MS) is well-documented (47). In fact, studies have shown that gut microbiota derived from individuals with multiple sclerosis can actually improve autoimmune diseases like autoimmune encephalomyelitis in rats (48). Notably, the composition of gut microbiota in multiple sclerosis patients differs significantly from that of healthy individuals. Specifically, multiple sclerosis patients exhibit lower levels of *Parabacteroides*, *Lactobacillus*, *Butyricimonas*, *Parabacteroides distasonis*, and *Actinobacteria* (49). Conversely, the abundance of *Methanobrevibacter*, *Akkermansia muciniphila*, and *Acinetobacter calcoceticus* is higher in multiple sclerosis patients compared to healthy individuals. This suggests that the manipulation of gut microbiota may hold promise in the treatment and prevention of multiple sclerosis (50).

Furthermore, the intestinal microbiota plays a crucial role in the formation of the myelin sheath in the frontal cortex of the brain, which is responsible for various cognitive functions such as attention, memory, learning, emotions, and feelings (51). Additionally, the intestinal microbiota serves as a protective barrier against the development of intestinal obstruction. When stress and depression occur, the intestinal wall becomes thinner and inflamed, allowing pathogenic microbes to directly stimulate the intestinal nervous system and mucosal immunity. This triggers a robust immune response and the production of pro-inflammatory mediators, which can ultimately affect the central nervous system (52). Supporting this hypothesis, the treatment of leaky gut syndrome with *Lactobacillus farciminis*, which also alleviates stress, has shown positive outcomes. An interesting case highlighting the connection between gut microbiota, brain function, stress, and depression is the reduced presence of Bacteroidetes in the feces of individuals with depression (53).

10. Mechanisms of action of microbiota on CNS

Various mechanisms have been proposed to explain the effect of microbiota on CNS. One of the mechanisms that several studies have addressed is the role of the vagus nerve. The Vagus nerve is responsible for controlling some vital actions such as controlling the heart and bowel movements. The vagus nerve also conveys peripheral immune status to the CNS. For example, it transmits inflammatory cytokines such as interleukin 1 (IL1) through nerve signals (54). Since the vagus nerve cut-off eliminates the regulatory effects of microbiota on cognitive functions, it can be concluded that vagus-dependent pathways facilitate the interaction of microbiota and the brain (55). It has been shown that cutting the vagus nerve even before microbial contamination is not able to prevent behavioral disorders in rats, so, as a result, a path independent of the vagus is considered to be effective. Since the intestinal microbiota can directly affect the immune system, the activation of the immune system can also be considered as a possible pathway in the relationship between the CNS and the microbiota (56).

The immune system plays a vital role in maintaining the homeostasis of the gastrointestinal tract, and during aging, a decrease in the function of the immune system, as well as a disturbance in the balance of the intestinal microbiota, can lead to behavioral changes and cognitive disorders. Behavioral changes in people with systemic infections, including intestinal infections, are proof of the interrelationship between the CNS and the immune system (57). In addition, gut microbiota and probiotics directly affect the brain by affecting inflammatory cytokines (58).

Studies show that the gut microbiota metabolites can regulate the maturation and function of microglia and thus affect CNS function (59). It has been shown that the gut microbiota plays an important role in regulating the permeability of the blood-brain barrier (BBB), which is a valuable defense system in protecting the brain from toxins (60). The function of BBB and microglia deteriorates with age, thus, these mechanisms can be a justification for cognitive disorders in the elderly (61).
Another possible mechanism is related to host energy metabolism and its close relationship with bacterial metabolites. Short-chain fatty acids,

which are mainly made from the fermentation of food fibers by intestinal microbes, play an important role in regulating the metabolism of free fatty acids, glucose, and cholesterol through G protein-coupled receptors(62).

Short-chain fatty acids participate in neural regulation through histone acetylation and their administration improves cognitive performance in laboratory animals (63). The next possible mechanism is the effect of microbiota on adults' hippocampal neurogenesis. The human brain has the ability to create new neurons in the hippocampus and lateral ventricles, this process is related to memory and learning, which is affected by many chronic diseases such as epilepsy, depression, Alzheimer's, and Parkinson's. The decrease in the ability of neurogenesis in the hippocampus also occurs in old age, which leads to cognitive disorders during this period. Recent studies have shown that intestinal microbiota can affect memory and cognitive abilities by influencing this process. Due to the existence of such metabolic and immune pathways, any disease that leads to primary dysbiosis of intestinal microbiota in childhood can cause permanent cognitive and behavioral disorders through the brain-intestinal axis (64). Many damages caused by disturbances in the balance of intestinal microbiota, such as changes in the function of the immune system or defects in the function of mitochondria and its metabolic complications, occur both in the stage of neurodevelopment and in neurodegenerative conditions caused by aging. Therefore, microbial disorders that occur in the early stages of life may not show their complications until old age (38).

Conclusion

The relationship between the brain and the gut is a bidirectional pathway. While the brain governs the functioning of the gut, the gut microbiota also has the ability to influence the brain. Through the production of various metabolites and the stimulation of different hormones, the gut microbiota regulates human behaviors and impacts the amygdala and hippocampus. Notably, the production of tryptophan by the gut microbiota plays a crucial role in serotonin production, leading to improvements in social behavior, stress, anxiety, and depression. Consequently, the intestinal microbiota holds promising potential in the treatment of nervous system disorders. It is therefore anticipated that the manipulation of the intestinal microbiota alone could prove effective in addressing conditions such as multiple sclerosis, schizophrenia, autism, Alzheimer's, and Parkinson's disease.

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