

Progress in the Application of Intestinal Flora in the Treatment of Depression

Zixin Li

School of Food Science and Technology, Hunan Agricultural University Changsha, Hunan,
410125, China

1260632600@stu.hunau.edu.cn

Abstract. Depression is a common mental disorder in modern society, which seriously threatens the mental health of patients. Many patients commit suicide because of it, which has a huge negative impact on families and society. There are many factors for depression. At present, research suggests that the composition of the gut microbiota is inextricably linked to the risk of depression. The brain and gut communicate with each other through the gastrointestinal tract and the nervous system, which enables the brain to adjust the local movement of the gut, and the function of brain is in turn influenced by the microbes in the gut. However, more experiments are needed to verify this conclusion. This paper mainly analyzes the mechanism of action between the brain and the gut between the gut and the brain, explores the connection between the two, and further analyzes the impact of the metabolites of the intestinal flora and neurotransmitters on the brain, so as to find the treatment of depression: Fecal microbiota transplantation and the intake of probiotics, as two new methods for the treatment of depression, can provide more accurate treatment for patients and solve the problem from the root cause. This article can provide some practical theoretical basis for related research. It is hoped that more researchers will be able to conduct more research in the future and make up for the vacancy of the experiment.

Keywords: GBA, depression, intestinal flora.

1. Introduction

Depression is a common mental disease. The lifetime prevalence rate of depression among adults in China is as high as 6.8 percent, according to the China Mental Health Survey, depression accounted for 3.4% of the total. Currently, 95 million people in China suffer from depression, and about 280,000 people commit suicide every year, 40 percent of whom suffer from depression [1]. Globally, around 1 billion people are living with a mental disorder and someone loses their life every 40 seconds due to suicide, with 77% of global suicides occurring in low - and middle-income countries [2].

There are many pathogenic factors for depression, such as family environment and congenital inheritance, but the pathogenesis is not clear. In a healthy human body, Bacteroidetes and Firmicutes are the dominant phyla, while the other phyla are relatively small. A relative balance is maintained among the species to maintain the normal operation of intestinal function. However, due to long-term stress, the balance between intestinal flora is broken in patients with depression. The abundance of Actinobacteria, Lactobacillus and other bacteria is significantly increased, while the number of Clostridium and Coprococcus is significantly lower than that of healthy people, this paper analyzes the relationship between gut microbiota and depression, mainly from the mechanism of brain-gut axis (GBA), metabolites and neurotransmitters of gut microbiota, and the methods related to bowel flora used in the treatment of depression: The GBA is a two-way transmission of information between the brain and the intestine. Microorganisms can exchange information and communicate with the central nervous system (CNS) through nervous and immune signaling mechanisms. The brain can also regulate the secretion function and local movement of the intestine. It can be seen that changes in the species of intestinal flora will have a certain impact on CNS, and it is speculated that fecal microbiota transplantation and the intake of probiotics may also be helpful for the treatment of depression. Clinical data have proved that taking probiotics can help restore the diversity of intestinal microorganisms, while FMT can reconstruct the intestinal ecosystem with normal function by transplanting feces from healthy donors into the gastrointestinal tract of patients, enriching the

microbial species, and achieving the treatment of depression. In summary, this paper hopes to open people's mind to depression treatment, in order to provide theoretical ideas for the scientists to conduct in-depth research in the coming days. However, the requirements for a sterile environment in the process of FMT transplantation are strict, and there is a lack of relevant trials. Probiotics can damage the immune function of immunocompromised people, so the amount of intake needs to be studied.

2. Correlation between Intestinal Flora and Depression

2.1. GBA Mechanism of Action

2.1.1 Brain-gut

Studies have found that the human brain and gut microbiota mainly establish bidirectional communication through the gastrointestinal tract (GI), enteric nervous system (ENS) and central nervous system (CNS), and several bidirectional communication routes (Figure 1) mainly include interaction with the nervous system, especially vagal afferents, host immune system regulation, and host immune system regulation. And the metabolism and production of small molecules including short-chain fatty acids and neuroactive compounds. These pathways closely connect the GI function and the CNS to form a complex and fine system called the GBA. In this large system, intestinal microbiota plays an important role. Studies have shown that intestinal microbes mainly regulate the GBA through the vagus nerve, immune system, neuroendocrine and microbial metabolites pathways [3]. Therefore, the GBA has been redefined as the microbiota-GBA. The brain can not only regulate the local movement of the intestine, the transport and secretion of the intestine, and the permeability of the intestine but also affect or regulate the community pattern and function of the intestinal flora of the whole autonomic nervous system (ANS) by directly regulating the luminal secretion of microbial gene expression hormones. The key intersection point of information communication between the gut and the brain is the CNS and the ENS. The ENS network is spread throughout the gut and receives biological, mechanical and environmental stimulation signals from the gut lumen, converts sensory signals into neural signals, hormonal signals and immune signals, and regulates the body's metabolic balance through two-way communication with the central nervous system. Intestinal microflora can interact with intestinal cells and stimulate the secretion of neurotransmitters or hormones to affect the brain and behavior. At the same time, microorganisms and their metabolites can indirectly influence the CNS through the ENS. On the other hand, the CNS can regulate the composition and function of the microbiota by affecting adrenergic nerve signals, regulating intestinal motility and intestinal endocrinology.

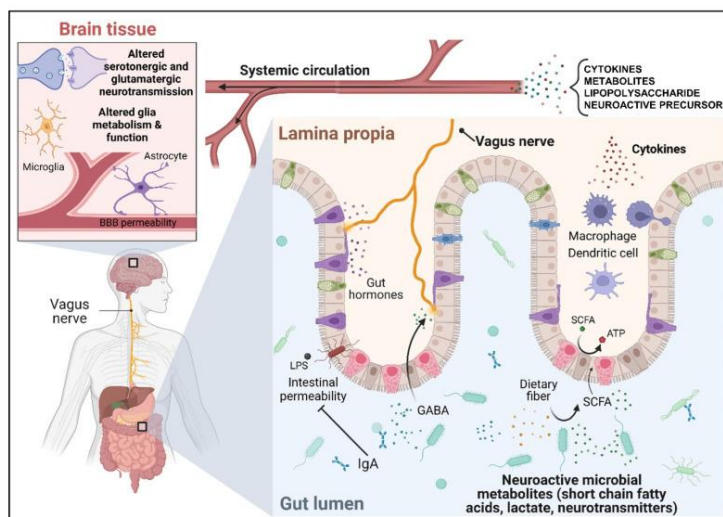


Figure 1. Summary of assumed mechanisms of information transfer between the gut microbiota and the brain [4]

2.1.2 Gut-brain

GBA mainly refers to the existence of a complex network structure between the GI and the brain system (including neuroendocrine and immune signaling pathways and direct neural mechanisms), the two through the brain to the gut and from the gut to the brain two-way pathways to play the role of mutual regulation, mutual response. The mechanism of action is as follows: the intestinal nerves composed of the submucosal and myenteric plexus organize the received information; Then the information of the changes in the internal is caught by the brain and spinal cord, and external environment transmitted by the CNS and integrate the information and finally act on the intestinal nerves to play a regulatory role, furthermore it can also directly regulate the gastrointestinal tract through the action of autonomic nerves. Neural signals can directly cause changes in brain function, and then have some effects on the regulation of intestinal nerves, immunity, and endocrine through the GBA. Conversely, abnormal signals in the gastrointestinal tract can also cause changes in brain function, leading to mental changes in patients. There is an axis between gut microbiota and the brain, called gut-brain axis, which can mutually regulate each other including ANS, ENS, CNS, HPA axis, etc. Gut microbiota and their metabolites are directly involved in mediating communication with biological barriers which include the CNS and the ENS, the barrier of intestinal mucosal and the blood-brain through neuroendocrine and enteroendocrine signaling pathways, or by parasympathetic and sympathetic components of the ANS and the ENS (mainly the HPA axis). The vagal afferent pathway can coordinate adaptive responses to various stressors and plays a vital part in activating the HPA axis. In addition, the gut microbiota can produce bacterial metabolites that act on the vagus nerve through tryptophan metabolism. HPA activation can stimulate the immune system, which affects inflammatory cytokines, alters them and increases the number of pro-inflammatory cytokines and chemokines.

2.2. Metabolites and Neurotransmitters Secreted by Gut Microbiota

2.2.1 Neurotransmitters

Some gut bacteria synthesize and release neurotransmitters, such as GABA, 5-hydroxytryptamine (5-HT), tryptamine, etc. Among them, the major excitatory neurotransmitter which is in the central nervous system is glutamate, the key factor responsible for anxiety-like behavior is the excitatory amino acids that are strongly associated with *Lactobacillus*. As the three major neurotransmitter systems in the brain, Norepinephrine (NE), Dopamine (DA), and 5-HT are all monoamine neurotransmitters, and their dysfunction may lead to the occurrence of depression. Studies have reported that only 5% of 5-HT in the human body exists in the brain, which is composed of 5-HT neurons in the central axis nucleus of the brain stem and can regulate a variety of functions such as emotion, learning, memory, and sleep, while the rest is synthesized by chromaffin cells in the gastrointestinal tract and released into the peripheral blood [5]. Each neuron can express several different 5-HT receptor subtypes, and a complex communication network is formed between multiple subtypes and different neurotransmitter systems. 5-HT_{1R} can negatively regulate the firing rate of neurons and the concentration of 5-HT in the synaptic gap. Stimulation of 5-HT_{2B} receptors can achieve similar effects as 5-HT reuptake inhibitors. Stimulation of 5-HT_{7R} affects the neurotransmission of DA, GABA, and glutamate, which also play unique roles in a variety of psychiatric disorders. In animal experiments, the serum concentration of 5-HT in germ-free mice was remarkably lower than that in the control group with traditional bacterial colonization, and *Lactobacillus* transplantation also significantly increased the amount of 5-HT-secreting chromaffin cells in the intestine of mice [6]. Abnormalities of the central dopaminergic system can affect a variety of brain functions such as emotion, perception, and behavior. Anhedonia is one of the most obvious characteristics of depression. As the most important neurotransmitter in pleasure perception behavior, the dysfunction of the DA system will have a greater impact on depression. A link between the system in the brain and depression was found earlier in mechanistic studies of drugs such as monoamine oxidase inhibitors. As a precursor of NE, the abnormality of DA energy system can affect the synthesis level of NE. The cell bodies of neurons synthesizing NE are mainly located in the locus

coeruleus, and the axons can project to the hippocampus, amygdala, thalamus and other brain regions. α 2-epinephrine can increase the density of auto receptors in the locus coeruleus neurons of patients with depression. After bifidobacterium transplantation into the obesity-induced mouse model, the original reduced NE level in the hypothalamus was restored to some extent, and the depressive-like behavior was also significantly reduced [7]. These lines of evidence confirm that gut microbiota is associated with changes in NE levels in the CNS.

2.2.2 Metabolites of gut microbiota

The human gut is home to millions of trillions of gut bacteria, which collectively form a stable gut system. Gut microbiota is not only closely related to human gastrointestinal health but also affects the growth and function of the CNS. For example, aiding food digestion, genetic background, sex, age, and producing micronutrients that the body cannot synthesize by itself is also one of the main functions of gut bacteria. Moreover, gut microbiota may also largely bear on brain development, so it is often called the "second brain". Bacteria can generate a lot of different types of neurotransmitters and bioactive substances. The primary bile acids (BA) produced by the gut microbiota form secondary BA and other metabolites that promote liver metabolism. The function of neurotransmitter receptors such as muscarinic acetylcholine and GABA can be controlled by BA, also it can prevent neurodegeneration [8]. Additionally, studies have found that the content of SCFA is bound up with the pathological mechanism of depression SCFA metabolites of intestinal flora are the main metabolites of digestible substances fermented by anaerobic microorganisms in the host body. Among them, acetic acid, propionic acid and butyric acid are the main representatives of SCFA with biological effects. Acetic acid can affect the expression of central neurotransmitter 5-HT, which is closely related to depression. Propionic acid could increase the number of gut-derived regulatory T cells and has a positive effect on the central nervous system by increasing myelin regeneration. Butyric acid can increase the concentration of central neurotransmitter 5-HT. In addition, it can not only promote the expression of brain-derived neurotrophic factor (BDNF) but also improve depressive like behavior in CUMS model mice [9].

3. Related Application of Microbiota in the Treatment of Depression

3.1. Fecal Microbiota Transplantation

3.1.1 Introduction

Gut microbiota is a complex and large bacterial community located in the human gastrointestinal tract. Studies have shown that changes in the composition of gut microbiota are connected with depression. Comparisons of intestinal flora between patients with major depression (MDD) and healthy controls, as well as studies of it based on animal models of depression, have shown several changes in the relative abundance of it in depressed animals, less bacteria such as *Lactobacillus* and *Bifidobacterium* were detected in the rats with depression after fecal microbiota transplantation (FMT) [10]. The quantity of the bacteria such as desulfurizing *Vibrio* and *Pilospirillum* increased [11]. It can be seen that fecal microbiota transplantation may be a treatment for depression. The process of transferring stool from healthy people into the gastrointestinal tract of depressed patients is called fecal microbiota transplantation so as to re-establish the intestinal ecosystem with normal function for patients to achieve the purpose of treatment. Compared with the popular antibiotic treatment and prebiotic intake, the benefits of fecal microbiota transplantation are more prominent, because antibiotics can make bacteria resistant and even damage the kidneys and other organs. Prebiotics can destroy the immune function of immunodeficient patients, so fecal microbiota transplantation is highly likely to become a new treatment for depression.

3.1.2 Potential mechanisms

It has been reported that FMT regulates proinflammatory factors and inhibits nervous system disease-related proteins and signaling pathways in the process of reshaping gut microbiota, such as

preventing NLRP3 inflammasome aggregation, down-regulating NF- κ B signaling pathway, and inhibiting α -synuclein and β -amyloid accumulation in the brain. Thus, it can alleviate the occurrence of inflammation [12]. FMT may reduce the levels of immune agonists such as microbiota metabolites such as LPS and peptidoglycan and inhibit their crossing of the blood-brain barrier, possibly by regulating immune-related proteins and signaling pathways, such as increasing the expression of CNTNAP4 and reducing the expression of TLR4, and by increasing the metabolic functions and pathways of gut microbiota metabolites such as tryptophan. Thus, the immune response of the body can be improved and the nerve can be protected [13]. FMT can alleviate the occurrence of oxidative stress in the body, reduce the levels of ROS and malondialdehyde, and increase the content of reduced GSH and the activities of antioxidant related enzymes such as peroxidase and SOD. It also improves the signaling pathways related to oxidative stress in the nervous system such as Nrf2 and MAPK, thereby reducing the symptoms of nervous system diseases. In nervous system diseases, intestinal microecological disorders induce intestinal inflammation and oxidative stress, reduce the emanation of short-chain fatty acids, cause changes in disease marker proteins (such as β -amyloid protein, tau protein [14], α -synuclein [15]), and eventually cause nervous system damage through the transmission and transfer of the GBA. Studies have indicated that patients with depression have significant changes in the constitution of gut microbiota, especially the abundance of fecal bacterium and cryptococcus, which is also significantly reduced in untreated patients with depression. The study found that fecal transplantation of depressed patients into germ-free rats showed behavioral and physiological characteristics of depression and abnormal tryptophan metabolism after one week. It is concluded that the abnormality of intestinal flora may be one of the important causes of depression.

3.2. Probiotics

Probiotics are a group of intestinal bacteria that are good for the parasitifer and have neuroprotective effects, which are widely used in the treatment of mental disorders. Clinical and animal experimental studies have confirmed that supplementation of appropriate amounts of probiotics can relieve depressive symptoms and have good therapeutic effects. The dominant phyla were Firmicutes, Actinobacteria, Proteobacteria and Bacteroidetes. The reported probiotics for the treatment of depression mainly include *Lactobacillus casei*, *Lactobacillus helveticus* and *Bifidobacterium*. The communication between the gastrointestinal tract (GIT) and the CNS is primarily facilitated by biochemical signaling pathways within the gut microbiota, which regulate the levels of circulating serotonin, kynurenine, tryptophan, and SCFA. Additionally, the gut microbiota influences both blood-brain barrier permeability and peripheral immune cell activation while also modulating brain microglia function. Dysbiosis, also known as changes in the gut microbiota, is more common in patients with chronic diseases such as metabolic syndrome and depression. When the composition of intestinal flora is damaged, the nature of its protective barrier is damaged, resulting in increased permeability of the intestinal wall, so that a large number of antigens invade the blood, and eventually cause a variety of inflammation. Then different kinds of substances will enter the CNS and change the physiological function of the brain. Firmicutes and Bacteroidetes dominate the healthy GI tract in adults. However, changes in diet, as well as increasing age, can lead to changes in the number of individual genera. For instance, the abundance of Bacteroidetes and Alistipes genera and choledochophila of Proteobacteria increased, and the abundance of Firmicutes decreased in association with a diet rich in protein and fat [16].

3.2.1 Probiotics in the form of live bacteria

Probiotic intervention in the form of live bacteria has a significant improvement effect on host depressive symptoms. It plays a role in immune, neurohormonal regulation, neurodevelopment and signal transduction pathways. In an animal experiment, *Clostridium butyricum* can significantly improve the depressive behavior of animals by stimulating the secretion of intestinal glucagon peptide 1 (GLP1), activating the brain GLP1 receptor and promoting the secretion of BDNF [17]. *Lactobacillus plantarum* PS128 can increase the levels of serotonin and DA neurotransmitter in the striatum of the brain. Daily intake of PS128 can help to improve the department of neuropsychiatric

disorders [18]; *Bifidobacterium longum* 1714 can significantly reduce stress and improve memory in healthy subjects by enhancing prefrontal cortex activity after 4 weeks [19].

3.2.2 Inactivated forms of probiotics

Studies of intracellular components of probiotics or inactivated bacteria have been shown to have antidepressant and stress-reducing effects. For example, studies of the antidepressant effects of live *Lactobacillus paracasei* NK12 and heat-inactivated bacteria found that after probiotic intervention in a mouse model of excessive CORT-induced depression, it was found that NK12 inactivated by heat treatment could still reduce the content of CORT in the hippocampus, and reverse the levels of BDNF, GC and its receptor proteins damaged in the model, and finally improve the depression-like symptoms of mice [20]. *Enterococcus faecalis* is a functional lactic acid bacteria recognized by the Japanese market. Heat-inactivated *Enterococcus faecalis* can reduce behaviors of anxiety and depression-like in mice, significantly, enhancing the expression of neurotransmitter receptor genes that involve *Adrb3* and *Avpr1a*, and the abundance of *Staphylococcus* and *Enterococcus* saw a relatively growing trend in the intestine.

4. Conclusion

There is a relationship between the decreased abundance of intestinal flora and depression. This article discusses how GABA is released through a complex network of neural, endocrine, and immune-mediated signaling pathways when multiple metabolites and neurotransmitters are released, which affects the intestinal function and brain function. Probiotics have become a potential therapeutic option for the treatment of depression by regulating the gut microbiome. Fecal microbiota transplantation can restore the balance of intestinal microecology by reconstructing the intestinal microbiome so that healthy intestinal flora can re-establish a stable ecological environment in the patient's body. However, what counts is that prebiotics and probiotics are not all necessarily the same, because the efficacy and safety of their treatment may vary depending on the number of doses used, the different strains, and the different preparations; Fecal microbiota transplantation has high requirements for the aseptic operation of the intestine, the selection of the donor and the transplantation bacteria.

The processing of the body requires a very strict design. In conclusion, it is hoped that the above methods can alleviate and improve the symptoms of depression, provide more theoretical support for the follow-up study of the correlation between specific flora and symptoms of patients with depression, offer new thinking for clinical practice in the future, and provide more individualized and targeted treatment strategies for patients with depression. Due to the lack of human experiments, there is still a lot of room for exploration. There are still some questions and working mechanisms that have not been answered, and further exploration is needed.

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