

The Effect and Potential Mechanism of Microbiota in Major Depressive Disorder

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Abstract. Nowadays, Major depressive disorder is a global mental illness, for which antidepressant treatment with traditional drugs in the past is not effective. Gut microbiota (GM) plays a vital role in depression. The diversity of GM differs between patients inflicted with major depressive disorder and normal people. Besides, GM disorder is closely related to depression severity. This study found that anxiety as the clinical manifestation of major depressive disorder is highly intertwined with GM. There is a reasonable hypothesis about the influence of sleep disorder on patients with major depressive disorder. In addition, the GM system is considered to be related with depression. Meanwhile, this paper not only reviews the potential mechanism of gut-brain axis bidirectional action, but also investigates the existing relief measures and antidepressant interventions related to GM, and providing new insights for the depression pathogenesis and GM as adjuvant intervention therapy.

Keywords: Microbiota; Major Depressive Disorder; Intervention; Hypothalamus-Pituitary-Adrenal.

1. Introduction

Major depressive disorder (MDD) is globally prevalent psychiatric disorders (Otte et al., 2016), which is usually characterized by depression and aversion to activities. According to the global survey, regardless of gender or age, 26.4 billion people worldwide are suffering or have suffered from MDD (Zhu et al., 2022). Thus, MDD has an overwhelming impact on global public health. However, the cause of depression is still unclear so far.

At present, there are several hypotheses to explain the potential mechanism of MDD. The monoamine hypothesis suggested MDD is caused by monoamine deficiency (Hirschfeld, 2000), while the dopamine hypothesis believes that potential dopamine in several depression subtypes can participate (Brown & Gershon, 1993). However, antidepressants produced according to the above hypothesis have not achieved their ideal effects (Boku et al., 2018). For example, they have, delayed effects, unsatisfactory curative effects, drug tolerance, and various adverse reactions (Bennabi et al., 2015). Hence, it is necessary to search for new potential pathogenic mechanisms and develop corresponding treatments for MDD.

With in-depth studies, researchers pay more attention to exploring the application of GM as a object for treatment, and microbiota-gut-brain (MGB) may provide insights. The latest research proves that GM shows great therapeutic potential in type II diabetes, autism, and Alzheimer's disease (Tang & Li, 2021). In addition, more studies have found that MGB has a significant impact on MDD. For example, the MDD show intestinal microflora disorder (Aziz et al., 2021). By sequencing the feces of patients with depression and comparing them with the healthy, their microbial composition changed apparently (Cheung et al., 2019). The gut-brain axis has two-way associations with the central nervous system (Konturek et al., 2004; Li et al., 2019; Zheng et al., 2016), which will manifest the feasibility of GM as adjuvant therapy.

Based on the existing findings, the GM's role in depression remission mechanism and antidepressant adjuvant therapy has been established, with more researchers committed to the application potential of GM in adjuvant therapy of MDD. However, the potential interaction mechanism between MGB and depression as well as how GM can be used as adjuvant therapy and intervention effect remains unclear. Thus, this paper not only reviews the differences between GM in MDD and normal people in the past, but also investigates the relationship between GM and clinical symptoms in MDD, and

the potential influence mechanism of MGB in MDD. Finally, it further discusses GM and focuses on the ways and functions of probiotics including Bifidobacteria in MDD adjuvant therapy, so as to foster new visions for MDD adjuvant therapy.

2. Differences of Gut Microbiota Between MDD Patients and Healthy People

Search in databases including Web of Science, Pub Med, Cochrane Library, and Science Direct with keywords such as “GM of MDD”, “GM of healthy people”, “influence of GM on MDD patients”, and “MDD microbiota”. Such keywords are retrieved from databases, essay names, keywords, abstracts, journals, and papers until June 2023. A total of 12 related literature have been retrieved and 4 experiments have been excluded, because the research subjects are usually mice rather than MDD patients. Other consistent experimental results demonstrate that the differences in GM between MDD and healthy people mainly exist in the diversity of microbial composition.

First of all, it is well known that various bacterial phyla in human guts share common habitats, and 70% of microbial groups come from the two most prominent phyla, that is, Bacillota and Bacteroides, while the number of Proteobacteria, Actinomycetes, Clostridium, and Verrucosa decreases (Eckburg et al., 2005). Compared with healthy people, MDD patients have various fecal microbiota compositions, which have increasing diversity of Bacteroides and Actinomycetes but decreasing diversity of Bacillota. It is worth noting that the levels of Enterobacteriaceae and Arismonia in MDD rose (Jiang et al., 2015). In the study (Jiang et al., 2015), even though gender variations have been reported in normal individuals, no significant differences between GM in female or male MDD patients. However, Naseribafrouei and his colleagues found that there was no difference in microbiota diversity (Naseribafrouei et al., 2014). The diversity of different research results may originate from various clinical representations of the subjects. Additionally, another study found Bacteroides, Proteobacteria, and Actinomycetes are overrepresented, while Bacillota is significantly underrepresented in severe depression (Jiang et al., 2019). In addition, compared with the control group, Enterobacteriaceae and Arismane are more abundant (Jembrek & Vlainic, 2015). Meanwhile, according to the research (Aizawa et al., 2016; Lin et al., 2017). Based on the analysis of existing studies, significant differences exist in GM diversity between MDD patients and healthy people.

3. Gut Microbiota and Clinical Symptoms in MDD Patients

3.1 Gut Microbiota and Depression Severity

Kazemi et al. (2019) made a comparative analysis of how probiotics supplementation affects the scores on the Baker Depression Scale (BDI), which proved that there was a significant difference in BDI scores between the groups after intervention. In the paired analysis, the average BDI score of the probiotic group decreased significantly. The reason for this result may be that there are several limitations in this test. First, there was insufficient fecal microbiota analysis. Secondly, interventions were conducted at different seasons, and participants were taking different antidepressants. In another similar experiment, the BDI scale was used to find the probiotic effect after 8 weeks of intervention in patients with MDD, which may be due to long dry expectation (Akkasheh et al., 2016). Various results suggest that probiotics is beneficial to depressive symptoms (Schaub et al., 2022). Moreover, the diversity and relative abundance of GM are improved by probiotic supplementation therapy, thus reducing the severity of MDD symptoms.

3.2 Sleep Disorders

Sleep disorder is related to MDD (Spiegelhalder et al., 2013). The recent meta-analysis provided that sleep time is related to the increasing risk of MDD (Zhao et al., 2015). Improving sleep conditions may prevent depressive symptoms. Studies have found GM can affect sleep. For example, Ogawa et al. (2020) manifested that the consumption of GM caused by antibiotic treatment led to the changing sleep/awakening structure as well as the gut balance of neurotransmitters. In addition, probiotic

treatment promotes sleep also supported by EEG evidence (Ho et al., 2021; Takada et al., 2017). The hypothalamus is affected by GM and some probiotics are considered to regulate activity of hypothalamus-pituitary-adrenal (HPA) (Takada et al., 2016). Although the subjects in the last three studies are not MDD patients, due to this functional association, it can be reasonably assumed that GM or its metabolites affect brain function, so as to improve sleep and regulate depression.

4. Potential Influence Mechanism Between Gut microbiota and Depression

This section, the possible mechanisms that GM on MDD are reviewed, including abnormal inflammatory factors, hormone disorders (cortisol), immune system. The relationship between GM and these factors was discussed.

4.1 Inflammatory Factors

Some hypotheses have linked inflammation to MDD pathogenesis, with emphasis on changes in the tryptophan metabolic pathway (TMP). The tryptophan is metabolized into 5-hydroxytryptamine and kynurenine, which is further metabolized into quinolinic acid with neurotoxicity. Studies have shown that the TMP of quinolinic and kynurenine acid is effected in MDD (ztürk et al., 2021; Ryan et al., 2020). These results indicate that neuroinflammation leads to the transfer of metabolic pathways and quinolinic acid can damage neurons (Pariante et al., 1999). These studies manifest that inflammatory factors have potential effects on MDD pathogenesis. Meanwhile, inflammatory factors can also trigger blood-brain barrier dysfunction (Liu et al., 2020; Rochfort et al., 2014; Wang et al., 2011). Therefore, intestinal barrier dysfunction leads to some harmful substances flowing into the brain and induces neuroinflammation (Kiecolt-Glaser et al., 2018). Besides, existing studies have confirmed that pro-inflammatory factors produced as inflammatory reactions of microbial pathogens during host infection can cause major depression symptoms in vulnerable individuals (Dantzer et al., 2008). This indicates that inflammatory factors are the mediators of MDD, and the dual effects of GM and inflammatory factors will aggravate the clinical symptoms of MDD patients.

4.2 Hormone Disorder

HPA axis changes in MDD, such as elevated cerebrospinal fluid corticosteroid releasing factor (CRF) (Dantzer et al., 2008). HPA axis is widely regarded as associated with stress response. More evidence shows that the MGB is related to the modulation of host stress response. In many other studies, the regulation of GM may affect stress response, including the HPA axis (Wu et al., 2020; Wu et al., 2021). The results showed that oral *Lactobacillus* strain Shirota (LcS; basonym, *Lactobacillus* strain Shirota) can induce the activity of vagus nerve afferent gastric branch, inhibit stress-induced increase of blood corticosterone, and restrain activation of corticosteroid-releasing hormone (CRH) positive neurons in rat hypothalamic paraventricular nucleus exposed to water, so as to avoid stress (Takada et al., 2016). These results prove that hormone disorder is highly correlated with MDD, and the MGB axis is also involved in the regulation of hormone response when GM shows a two-way influence in hormone response.

4.3 Immune System (Blood Brain Barrier)

The Blood-brain barrier (BBB) separates the central nervous system from peripheral blood (Daneman & Prat, 2015). Microbial destruction of brain barrier dysfunction can trigger many related diseases (Diaz Heijtz et al., 2011; Fiorentino et al., 2016; Holmqvist et al., 2014), although the exact mechanism of microbiota affecting the BBB physiology is still unclear. However, according to rodent models, the loss of normal GM led to an increase in BBB permeability, while pathogen-free GM restored BBB function (Braniste et al., 2014). Thus, GM imposes related influence mechanisms on BBB, which possibly include gut-derived neurotransmitters and bacterial metabolites regulating BBB.

5. Treatment Scheme of MDD Based on Gut Microbiota

The above-mentioned results indicate GM makes a difference in hormones, anxiety, and depression. Through the enteric nervous system with the central role, the existence of the brain-gut axis and its two-way connection are confirmed, indicating that GM may be effective in the treatment of MDD. Although carefully designed clinical trials are needed to reach a clear conclusion, the following focuses on fecal transplantation and oral probiotics.

5.1 Fecal Microbial Transplantation

Fecal microbial transplantation (FMT), a method to transfer fecal bacteria from the healthy to patients. Previous studies have shown that FMT can induce depression (Kelly et al., 2016; Zhao et al., 2020). However, FMT is rarely used in mental illness treatment up to now. Meanwhile, FMT plays an important role in tackling microbial structural disorders (Bakken et al., 2011) and depression (Fond et al., 2020; Rao et al., 2021) with excellent results, such as restoring the normal metabolism of the host (Yan et al., 2018). Geng et al. (2018) proposed that FMT can regulate the diversity of microbiota, reduce intestinal epithelial verification response and host inflammatory response. Hence, FMT adjuvant therapy can affect and improve MDD symptoms in various aspects.

5.2 Oral Probiotics

As for the types of probiotics taken, most studies adopt the form of compound probiotics. Schaub and his team (2022) conducted a research on probiotics and treatment for patients with depression, taking probiotic supplements, which contains 8 different strains. The daily dose contains 900 billion CFU/day, with special attention paid to the fact that the probiotic effect is only significant in subsamples with high compliance after 8 weeks and aggravation during follow-up. Therefore, the remission rate of the probiotic group is 55%, while that of the placebo group is 40%. The results show that probiotic treatment can not only improve depressive symptoms and maintain healthy intestinal type, but also retain species richness and increase specific health-related bacterial groups. The following experiments also confirmed the above conclusion. Pinto-Sanchez et al. (2017) studied the effect of probiotic powder supplementation on the IBS patients, which found that patients with more probiotic powder supplementation showed a decrease in depression score. However, according to functional magnetic resonance imaging analysis, various probiotics responded less to negative emotional stimuli in multiple areas of the brain than the placebo group. In the subgroup with high depression index at baseline, compared with the placebo-controlled subjects, probiotic intervention subjects had significant improvement in depression (Otaka et al., 2021).

6. Conclusion and Prospect

In addition to reviewing the differences in GM between MDD and healthy, this paper summarizes the potential mechanisms between MDD and MGB. At the same time, various studies have found that there were differences between MDD and the healthy, which are bidirectional related to the clinical manifestations of MDD. For example, depressive symptoms lead to an imbalance of intestinal microbial homeostasis. On this basis, the destruction of intestinal microbial diversity further aggravates the disease. The potential mechanisms of the MGB axis for MDD are mainly inflammatory factors, hormone disorders, and the immune system, such as microbial destruction of BBB. These studies further demonstrate the feasibility of intestinal microbial intervention and emphasize the importance of intestinal microbial intervention as adjuvant therapy for depression. However, given that MGB and MDD are still in the preliminary research stage with insufficient samples, there is not much related research on the intervention scheme of reverse regulation of GM through the MGB axis and the treatment of intestinal microbial differences related to probiotics.

The future research of MGB and MDD can be based on the difference between MDD and normal people's GM. Since the previous research on probiotics as antidepressant adjuvant therapy focuses on the overall effectiveness, with the further development of future research, we can discuss the

measurement of probiotics in anti-MDD adjuvant therapy, combination accuracy of specific types, and whether the synergistic effect can be widespread or whether the beneficial effect of probiotics depends on specific antidepressant drugs. Besides, new intervention schemes need to be explored, such as stimulating the brain (transcranial DC stimulation, transcranial magnetic stimulation, and transcranial AC stimulation) and using the two-way connection of MGB to change the composition of GM, so as to achieve the intervention on MDD. It is hoped that new insights and promising treatment methods will be brought to depression treatment through these efforts.

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