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Research Progress of Improving MDD by Fecal Microbiota Transplantation Affecting Intestinal Microbiota-Gut- Brain Axis

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Abstract: It has been improved that fecal microbiota transplantation (FMT) can alleviate gastrointestinal disorders such as Clostridium difficile infection (CDI). Moreover, some studies have also concluded that FMT is available in alleviating Major Depressive Disorder (MDD), also known as depression widely, by regulating microbiota-gut-brain axis (MGBA), hence, this paper summarized the relationship between MGBA and MDD and mechanisms of MDD which is related with MGBA. And this review retrospected the animal experiments and clinical studies on the treatment of depression with FMT in recent years and discussed the future development of FMT, in order to assess whether FMT is potential and credible in the treatment of depression.

Keywords: FMT; Depression; Intestinal Flora

Background

Depression is the fourth largest disease in the world, but at present, the general public's cognition and prevention of depression is still in a vague stage, and the development of related drug research and development and treatment methods is also gradually stalled[1]. In recent years, with the development of science and technology, fecal microbiota transplantation (FMT), as a new treatment method, has been gradually applied in the diagnosis and treatment of various diseases, among which depression is one of the main indications. Fecal microbiota transplantation (FMT), which means transplanting the functional gut flora in the feces of healthy people into the gastrointestinal tract of the patient to rebuild new intestinal flora and realizing the treatment of intestinal and extraintestinal diseases, is currently used for the identification of Clostridium difficile Bacillus infection and other important methods for various flora-related diseases. Therefore, the disorder of intestinal will cause the occurrence of many diseases, one of these diseases is depression, that patients with depression will concomitant the symptom of increased levels of enterobacteriaceae or rijcidaceae, and decreasing levels of faecalis in the gastrointestinal tract during is also a significant sign of depressive appearance.

1. Relationships between MDD and intestinal microbiota-gut- brain axis

Gut microbes can interact with the brain in three particularly important ways: 1) Directly through the vagus nerve and the neural network that surrounds the gut and sends signals to the brain; 2) through immune cells that reside in the gut and travel to the brain;3) Metabolites produced by gut microbes first enter the blood, then the brain, and ultimately affect behaviori. Certain metabolites of gut bacteria can cause anxiety and autism-related abnormalities when injected into functioning mice. This further supports the possibility that microbial metabolic molecules link brain, gut, and neuro-emotional circuits in the neuroendocrine metabolic stress response system. The microbiota-gut-brain axis (MGBA) connects the central nervous system, gastrointestinal tract and gastrointestinal microbes through the above-mentioned approaches to regulate each other and jointly maintain body balance. Generally speaking, it can be roughly divided into five ways, namely, autonomic nervous system (ANS), hypothalamic-pituitary-adrenal (FPA), immune system, enteric nervous system (ENS) and circulatory system[2]. Any functional disorder of MGBA may induce the occurrence of depression. On top of that, the "leaky gut" hypothesis has also been linked to depression[3].

2. Technology of fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a highly efficacious and wide-used modality to treat recurrent or refractory infection (CDI), with overall curative radio of 90%. Therefore, FMT has been widely used for around 10 years[4]. The core technology is to extract beneficial bacteria from the feces of healthy people after centrifugation and filtration and transplant them into the gastrointestinal tract of patients, so that the gastrointestinal flora of patients can be remodeled and play a normal function, and then treat diseases related to intestinal flora disorder[5].

3. FMT animal models applied to MDD

Zheng[6] et al isolated and extracted feces from healthy control group (n = 5, male, 29-62 years) and MDD patients (n = 5, male, 27-61 years) and transplanted the flora into adult (6-8 weeks old) KM mice in order to determine whether intestinal flora can transmit depression and whether the mice were prone to depression. Two weeks after fecal microbiota transplantation, depression levels of mice in model group were assessed by a series of behavioral tests, including Open-field test (OFT), Y-maze test, Tail suspension test (TST) and Forced swimming test (FST), in both the model and control group. The final results showed that the lack of gut microbiota resulted in a reduction in immobility time in FST, and no difference was found in the total distance travelled between GF and SPF mice from the OFT. On the contrary, compared with SPF mice, the proportion of central movement distance in GF mice increased significantly ($P \geq 0.05$), indicating that the anxiety-like behavior of GF mice decreased, and GF mice showed better memory performance compared with SPF mice. In addition, by measuring the fecal flora content of the two groups of mice, it was found that the gastrointestinal bacterial phenotype of MDD mice was significantly different from that of healthy mice, and was consistent with the bacterial phenotype of their respective donors. This finding suggests that gut microbiota may influence the microbial-gut-brain axis by altering gastrointestinal metabolism, thereby "passing on" depression.

Schmidt[7] et al. gave intestinal flora of healthy SD rats that had suffered from spinal cord injury (SCI), and conducted behavioral experiments such as high plus maze (HPM). The results showed that transplantation of FMT from healthy rats to SCI induced depressed and anxious rats significantly reduced depressive and anxiety-like behaviors. These results suggest that fecal bacteria in healthy FMT rats can significantly improve SCI induced depressive behavior.

The use of FMT therapy in healthy and depressed mice demonstrated that FMT can cause depression in healthy mice, that means FMT can also be used as a new way to treat depression.

A series of animal experiments are listed above. Whether FMT is applied to healthy mice or depressed mice, it is used to induce depression or fight depression by interfering with the intestinal flora of experimental animals. While the exact mechanism by which FMT improves depression is unclear, it is undeniable that the microbial-gut-brain axis plays a large role.

4. Clinical application

Huang[8] et al. used FMT to treat 30 patients (18 males and 12 females, with an average age of 44 years) with refractory Irritable Bowel Syndrome (IBS), for 2 - 3 times of FMT stage treatment. Ibs-qol, IBS-SSS, GSRS, HAM-A and HAM-D scales were used to score the patients 1 and 3 months after FMT administration, and the results showed that gastrointestinal symptoms were significantly improved while depression and anxiety symptoms were alleviated.

Up to now, there is no clinical research data on the treatment of simple depression with FMT, most of which are similar to the above study. Although the mechanism of FMT improving depression is discussed and other disease factors interfere. Except for mental symptoms are significantly improved, there is no definite evidence that FMT can directly affect the depression of PATIENTS with IBS[9].shape

5. Discussion

At present, FMT is still in the stage of theoretical research, and it is still unknown when it can be really applied in clinical practice. Nevertheless, this kind of technology still shows great potential in the field of mental illness treatment, changing the inherent "stopgap treatment" of the traditional treatment thought, provides a new idea for the treatment of depression. It is hoped that more researchers will focus on this technology in the future, so as to overcome technical barriers and benefit patients as soon as possible.

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