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Research Advances in Probiotics and Depression

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Abstract

Depression is a common mental illness characterized by continuous and long-term low mood. In recent years, with the increasing number of depression-related research, a growing body of research suggests that dysbiosis of the intestinal flora is associated with the development of depression. Probiotics can effectively improve intestinal flora disorders and repair gastrointestinal function, which is expected to become a new treatment for depression. This review summarizes the studies related to probiotics and depression.

Keywords: intestinal flora, probiotics, depression

1. Introduction

Depression is a common mental illness characterized by continuous and long-term low mood, and it has become the fourth largest disease in the world. In addition, the incidence of depression has begun to become younger. Drug treatment is the main treatment of depression. Domestic and foreign studies show that the effective drugs for treating depression are mainly divided into tricyclic antidepressants (such as imipramine, clomipramine, etc.), serotonin reuptake inhibitors, and other new antidepressants (such as fluoxetine, Renaissance, etc.) (Liang S, Wang T, Hu X, et al., 2015; Correia MI, Liboredo JC, Consoli ML., 2012; Wang H, Lee IS, Braun C, et al., 2016). However, medication generally takes effect after 10-14 days and does not adequately achieve symptom relief and functional recovery (Sharon G, Sampson TR, Geschwind DH, et al., 2016). In addition, the US Food and Drug Administration has proposed that antidepressants can have adverse effects on children and adolescents and should be used with caution.

The gut microbiota is an integrator of neurological development and function, and is a lever for mental health and disease (Sharon G, Sampson TR, Geschwind DH, et al., 2016). The gut microbiota plays a role in neurogenesis, while also regulating many behaviors in animals. Studies of behavior and insulin action in dietary obese mice revealed that changes in the gut microbiota can control brain insulin signaling and metabolic levels, which subsequently affect neurobehavioral changes (Soto M, Herzog C, Pacheco JA, et al., 2018). At present, related studies of microecology have involved depression (Peng Z, Ying W, Liang C, et al., 2013), Multiple sclerosis (MS) (Jangi S, Gandhi R, Cox LM, et al., 2016), Parkinson's disease (PD) (Scheperjans F, Aho V, Pereira PA, et al., 2015), Alzheimer's disease (AD) (Zhuang ZQ, Shen LL, Li WW, et al., 2018). And other central nervous system diseases. Recent studies show that, in anxiety, depression, cognition, and autism spectrum disorders, there has communication between the intestine and the brain (Sharon G, Sampson TR, Geschwind DH, et al., 2016). This review summarizes the research progress between probiotics and depression.

2. Possible Mechanisms by Which Intestinal Flora Affect Depression

The intestine is called the "second brain", and the "brain-gut" axis bidirectional regulation theory has been confirmed by laboratory and clinical studies (Keightley PC, Koloski NA & Talley NJ., 2015). In recent years, intestinal flora has played a key role in the "brain-gut" axis. The ability of regulating behavior by communication between intestinal flora and brain is becoming more and more important in affecting health and disease (Cryan JF & O'Mahony SM., 2011; Flight MH., 2014).

The intestine microbiota regulates the development and function of the enteric nervous system and central nervous system. Intestinal movement, local blood flow and gastric acid secretion are regulated by the enteric nervous system that is very important when the information exchange happens between the brain and the intestine (Furness JB., 2012). The maturation of the enteric nervous system in the intestine must depend on the presence of the intestine microbiota which plays an important role in regulating enteric neurogenesis, axonal growth, neuronal activity and the supply of glial cells to the lamina propria. Important processes of the central nervous system include glial cell function, myelin formation, neurogenesis, blood-brain barrier function and neuronal activity, which is regulated by the intestine microbiota. Among them, glial cells are interconnected with neurons and regulate neuromodulation, endostosis, metabolic and immune mechanisms and it is also highly related to neurogenesis, neuronal plasticity, neuronal pruning and stripping. Intestinal flora control microglia maturation and function, and also influence oligodendrocyte function and myelination. During the critical period of neurodevelopment, cortical myelin formation is dependent on gut microbes, which determine the expression of myelin formation-related genes (Rudzki L & Maes M., 2020).

In the studies on the pathogenesis of depression, the most widespread and accepted hypothesis is the monoamine neurotransmitter hypothesis. And decreased levels of monoamine neurotransmitters or synaptic dysfunction is the biological basis of depression. Currently, most first-line antidepressants have been developed on the basis of the monoamine neurotransmitter hypothesis. Neurotransmitter content is closely related to the homeostasis of the intestinal microbiota, which is an important regulator of human neurotransmitter production and synthesis. In the imbalance of intestinal microflora, neurotransmitters are abnormally expressed. The abuse of antibiotics can lead to disordered flora and reduced synthesis of neurotrophic factors such as neurotransmitters, which can affect mood and exercise and increase the risk of depression.

Depression is associated with hyper-activation of the hypothalamic–pituitary–adrenal axis (HPA), which is directly link to intestinal flora. Early in life, intestinal flora plays an important role in the changes of the HPA axis. Studies have shown that transient gastric stimulation during the neonatal period can lead to prolonged depression and increased anxiety-like behavior. It is manifested by an upregulation of hypothalamic pro-adrenocorticotropic hormone-releasing hormone expression (Liu L, Li Q, Sapolsky R, et al., 2011). Pro-adrenocorticotropic hormone-releasing hormone induces the secretion of pro-adrenocorticotropic hormone from the anterior pituitary gland and promotes glucocorticoid release, and persistently elevated glucocorticoid and pro-adrenocorticotropic hormone levels lead to a disruption of the negative feedback mechanism of the HPA axis.

The stressful state leads to dysbiosis of the intestinal flora, causing increased expression of pro-inflammatory cytokines that include mainly interleukin-6 and γ interferon. The inflammatory state can alter intestinal permeability and lead to increased release of inflammatory factors. Canine urine pathway toxic metabolites and inflammatory factors can lead to blood-brain barrier damage, with increased expression of interleukin-6, interleukin-1 β, and nucleotide-binding oligomerized structural domain-like receptor protein 3 inflammatory vesicles. It has been found that nucleotide-binding oligomerized structural domain-like receptor protein 12 inflammatory vesicles are key mediators of stress-induced neuroinflammatory responses and their dysregulation may be associated with the pathophysiology of depression (Akosile W, Voisey J, Lawford B, et al., 2018). The immune system and the regulation of the microbe-gut-brain axis are protective against stress responses. The study of Westfall and Pasinetti (Westfall S & Pasinetti GM., 2019) has demonstrated that Lactobacillus plantarum can inhibit the production of interleukin-1β, which is mediated by nucleotide-binding oligomerization structural domain-like receptor protein 3, in microglia. Thus, consumption of polyphenolic foods containing Lactobacillus plantarum reduces chronic stress-induced depression-like behavior.

Intestinal microbiota can also regulate host health through other pathways. Intestinal microbes are closely related to mitochondria. On the one hand, Intestinal microbes can regulate the transcription of genes in mitochondria, such as peroxisome proliferator-activated receptor γ coactivator-1α, silencing regulatory protein 1 and AMP-dependent protein kinase, and influence mitochondrial energy metabolism, reactive oxygen species production and inflammatory responses (Lin X, Chen Y, Zhang P, et al., 2020). On the other hand, mitochondrial biological processes influence the function of intestine in mucosal barrier, immunity and microbiota composition. The intestinal mucosal barrier and the blood-brain barrier can be disrupted by the changes of intestinal microbes (Marungruang N, Arévalo Sureda E, Lefrançoise A, et al., 2018). Intestinal microbes affect the Central Nervous System (CNS) by triggering inflammation, oxidative stress and mitochondrial dysfunction (Abautret-Dalyá, Dempsey E, Parra-Blanco A, et al., 2018).

3. The Role of Probiotics in Depression

Probiotics are a class of living microorganisms. When taken in sufficient doses, they can have a positive effect on the health of the organism. This positive effect may be useful not only for the gastrointestinal tract, but also for the entire microbial-gut-brain axis (Tao Weiwei, Dong Yu, Liu Li, et al., 2019).

The research of Martin (Martin-Subero M, Anderson G, Kanchanatawan B, et al., 2016) showed a significant reduction in time through the cross maze after feeding probiotics to depressed model mice. Studies have found that mice with knockout of fat mass and obesity-related gene (Fto) show increased abundance of Lactobacilli and low content of Porphyromonas and snails, and behaviors of anxiety and depression can be reduced by these changes in the intestinal microbiota (Sun L, Ma L, Zhang H, et al., 2019). In investigating the potential correlation between symptoms of depression and fecal metabolites in CUMS rats, Li et al (Li J, Jia X, Wang C, et al., 2019) found that altered intestinal flora may affect symptoms of depression in CUMS rats through altered intestinal metabolites. In contrast to rats without specific pathogens, germ-free rodents transplanted with the fecal microbiota of depressed patients will show depressive-like behavior (Yang Z, Li J, Gui X, et al., 2020). These animal studies mentioned above suggest that probiotics can alleviate depression or assist in the treatment of depression.

In a randomized double-blind placebo human clinical trial, compared to the placebo group, depressive and anxious behaviors were significantly reduced after 30 days in the control group that was given Lactobacillus ROO52 and Bifidobacterium longum R0175 (Messaoudi M, Violle N, Bisson JF, et al., 2011). And study of Messaoudi et al (Messaoudi M, Lalonde R, Violle N, et al., 2011) showed that depression-related scales of volunteers receiving oral probiotics decreased. It indicates that oral probiotics improved depression-like symptoms. Slykerman et al (Slykerman RF, Hood F, Wickens K, et al., 2017) found that in pregnancy and postpartum, postpartum depressive symptoms of pregnant women supplemented with Lactobacillus rhamnosus HN001 decreased. A large amount of evidence shows that depressed patients have obvious intestinal flora disorders, manifested by a decrease in bacterial diversity and a significant change in the relative abundance of bacteria (Ke Chengren & Ye Lanxin, 2021). In addition to standard treatment, patients with probiotics (such as C. butyricum MIYAIRI588) can effectively improve the flora disorders of patients with depression, resulting in a significant antidepressant effect (Miyaoka T, Kanayama M, Wake R, et al., 2018; Reininghaus EZ, Platzer M, Kohlhammer-Dohr A, et al., 2020).

4. Discussion

As the global research on probiotics has their beneficial effects, whether for depression or anxiety, probiotics supplementation may be a new method or adjuvant treatment for mental disorders, but due to the relative lack of research, the specific mechanism of action needs to be further explored.

Although mood disorders are associated with changes in probiotics, clinical studies on probiotics and depression are currently very scarce, and one limitation is the lack of specific microbiota criteria. Probiotic expression is influenced by the host, age, food, environment, antibiotics, as well as genetic factors. At the same time, relevant studies also found that the effect of probiotics on cognitive function is still controversial, and it is difficult to extrapolate the animal experimental results to the population, which may be related to the strain / strain specificity of probiotics. The ability of probiotics to improve the host cognitive decline requires large-scale clinical trials and possible mechanistic analysis at the strain level. It is also recommended that psychiatrists understand patients' eating habits and prepare new tools of microbiology, genetics and bioinformatics in mood disorders research in order to better serve clinical psychiatry.

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