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To Explore the Pathogenesis and Treatment Progress of Post-Stroke Depression Based on the Microbe-Gut-Brain Axis

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Abstract: Post-stroke depression and Post-stroke depression (PSD) has seriously affected the cognitive recovery, neurological rehabilitation, and the improvement of life quality in patients after stroke. In recent years, many studies found that the regulation of microbial-gut-brain axis can provide new ideas for treatment, intestinal flora is a key factor to regulate the brain gut axis signal pathway, through the PSD pathogenesis regulate brain neurons, endocrine system, metabolism and immune system pathway, keep the two-way communication between the brain and gut, alleviate depression behavior. The stroke-depression-stroke relationship proves that stroke can further develop depression, and depression can increase the risk of stroke recurrence and death. Most patients with PSD have poor compliance to traditional antidepressants and urgently need to explore more effective treatments. Based on the understanding of intestinal flora, this paper is based on the influence of intestinal flora changes and PSD in the brain-gut axis. The aim is to explore the potential relationship between the pathogenesis of stroke depression and the brain-gut mechanism, and to provide new ideas and reference for the diagnosis and treatment of PSD.

Keywords: Post-Stroke Depression; Microbe-Gut-Brain Axis; Pathogenesis; Intestinal Microflora

1. Introduction

Post-stroke depression (PSD) is the most common and serious post-neuropsychiatric complication of stroke. It is manifested as secondary depression with poor mood, slow thinking, slow response, and even suicidal tendency, often accompanied by a series of somatization symptoms such as poor sleep, dizziness, defecation disorder and physical sleepiness. The incidence of PSD reached 31% within 5 years of stroke, 33% within 1 month and 34% within 1 year, and the mortality rate was several times higher than that in non-PSD patients[1]. PSD greatly the neurological function of patients after stroke [2] , extends the treatment and rehabilitation time, and reduces the quality of life. Therefore, the early diagnosis and intervention of the disease have important clinical significance. Now found that microbial-brain-gut axis research is closely related to PSD disease, through consulting relevant literature, summarizes microbial-brain-gut axis of Chinese and western medicine research, contact the pathogenesis of depression after stroke, overview of intestinal microbiota in the treatment, for clinical application of traditional Chinese medicine to provide some new ideas and methods.

2. Microbe-gut-brain axis

The brain-gut axis is the regulatory pathway that exists between the nervous system and the gut, It includes the central nervous system, endocrine system, enteric nerve and autonomic nervous system. Some gastrointestinal signals can affect the cognitive function of the brain through the brain-gut pathway, including emotion, learning and so on. In this pathway, gut microbes can regulate the brain-gut axis. In the homeostatic or pathological state, the gut microbiota releases and regulates metabolites and neurotransmitters, and the dysbiosis or ecological imbalance can further aggravate central nervous system diseases, so the brain-gut axis is redefined as the microbe-gut-brain axis (Microbiota-gut-brain Axis, MGBA)[3]. Many studies have proved that the gut microbiota is indispensable in the brain-gut axis, gut microbiota can by neurons, immune signaling pathway and nervous system communication, can reduce inflammation after brain injury, improve the body immunity, regulate the hypothalamus-pituitary-adrenal axis (HPA), enhance neurotransmitter secretion function, etc[4].Microorganisms that colonize the intestinal mucosal tissue produce immune-inflammatory signals[5], Activate and stimulate the central immune hypothalamic-pituitary-adrenal axis (Hypothalamic-pituitary-adrenal axis, HPA) hyperactivity stimulates the release of cortisol, increase intestinal proinflammatory factors, participate in the regulation of neuroimmune inflammation in the brain, a large number of enteric nerves in the intestinal wall, intestinal information to move the brain, regulate the brain function.

3. Progression of PSD

At present, the specific physiopathological process and causes of stroke depression are not clear. The persuasive pathogenesis includes neurotransmitters, immune, endocrine mechanisms and neurotrophic mechanisms to participate in the pathogenesis of post-stroke depression.

Among the many regions of the brain involved in emotional regulation, the prefrontal cortex and amygdala can affect the regulation of neurotransmitters through the release of norepinephrine and 5-HT, and the imbalance of neurotransmitters in the brain may lead to depression[6]. The prefrontal cortex is the key to regulate the emotional cognitive activity, with a high probability of depression in the brain areas damaged by ischemia and hypoxia. The periknee anterior cingulate cortex activation was increased in poststroke depression, and the bilateral amygdala and dorsal anterior cingulate cortex activation were decreased. In addition, information transmission factors between effector cells and nerve cells are monoamine neurotransmitters, which are radiated to the hippocampus and frontal areas through the basal ganglia and thalamus to regulate the body's cognition, emotion and physiological activities[7]. The necrosis of nerve cells produced after stroke can reduce the neurotransmitter level and the peripheral sympathetic nerve excitability in stroke patients.

The immune system is a bidirectional communication pathway between the center and the periphery after stroke, and the imbalance between proinflammatory factors and anti-inflammatory factors leads to neurological deterioration. Cytokines are humoral mediators of innate and adaptive immunity and are also important regulators of mood[8]. After ischemic stroke, its secretion will be significantly increased, leading to the activation of indorelamine 2,3-dioxygenase in glial cells, reducing the bioavailability of tryptophan, hindering serotonergic transmission, producing neuroactive tryptophan metabolites, and ultimately causing depression. Recent studies indicate that microglial neuroinflammatory pathological processes[9], Secretion of proinflammatory factors further cause or aggravate nerve injury or brain parenchymal injury, microglia contain a large amount of IDO, together participate in the regulation of depressive-like behavioral process. After brain injury of ischemic stroke, in a very short time, microglia activate and concentrate to the injured lesion site, releasing cytokines, such as interleukin-1 β and tumor necrosis factor- α, which are potentially causing nerve excitation and aggravating neuroinflammation. Despite the lack of a complete physiopathological explanation for depression, inflammation remains a driver of its development and an important biological factor increasing the risk of onset depression.

The HPA axis is the main neuroendocrine system that regulates mood. When the hippocampal tissue or other signals reach the hypothalamus, the paraventricular nucleus tissue releases corticotrophins, which later further synthesize and release adrenocorticotropic hormones and glucocorticoids[10]. Studies have shown that HPA axis hyperactivity is the main cause of post-stroke depression. Mediation of 5-HT can regulate depression, HPA activates negative feedback mechanism, and hormone homeostasis imbalance. The cortisol concentration can be increased after detecting saliva and blood of depressed patients. Higher serum levels of interleukin-6 and cortisol in the early stage than in non-PSD patients[11], To confirm the interrelationship between cortisol content concentration and PSD, but the specific relationship should be clarified further. The 5-HT gene polymorphism is associated with increased cortisol, making post-stroke patients more susceptible to depression in the face of low quality of life stress.Neurotrophic factor is responsible for neuronal growth and development, axial synapses, and synaptic plasticity, and is particularly important for ischemic stroke recovery and neurorehabilitation. Brain-derived neurotrophic factor (brain derived neurotrophic factor, BDNF) is produced by glutamate and glial cells, and is significantly expressed in many brain areas such as hippocampus, cerebral cortex and basal segment. It has the function of regulating neuronal differentiation and development, can improve body learning and cognitive function, and is closely related to depression and anti-depression[12]. BDNF secreted factors after synapses, which can affect serotonergic and dopamine transmission, are essential for synaptic transformation of synaptic memory by regulating synaptic activity[13], Among the most widely distributed and widely studied mammals, hippocampal neurons show reduced proliferation and differentiation in rodent animal models of depression, causing depressive-like behaviors that directly affect monoamine levels and behavioral function in rats. Chen Yan et al[14]To explore the mechanism of miR-98-5p in mice, targeting BDNF to improve depressive behavior in the hippocampus.

4. Association between MGBA and PSD

Guinal flora microbial species aggregation, can maintain intestinal balance, body nutrition and metabolism level. Through the detection of 12 kinds of intestinal flora, it was found that the flora was different between stroke patients and PSD patients, which was mainly

manifested by the increase of the composition ratio of potential pathogenic bacteria such as Klebsiella and Enterobacter, and the decrease of the content of beneficial anti-inflammatory bacteria[15]. PSD patients intestinal flora diversity, but the flora abundance decreased, most of the species decreased, and considered the metabolic disorder; after stroke, intestinal immune mechanism and flora metabolism jointly produce neurotransmitters, participate in PSD progress; fecal bacteria transplantation animal test and clinical studies proved that intestinal flora disorder, aggravate depression-like symptoms[16].The increase of harmful intestinal colonies can induce mental disorders, activate the HPA axis and immune function reactivity, cause intestinal inflammation, and lead to impaired nerve function from bottom to up.

Pathpathological 5-HT imbalance in patients with PSD is closely related[17], The intestinal flora and the body coexist, affect the development and maturity of the intestinal nervous system, maintain the body health. The number and composition of the intestinal flora or its metabolites can affect the cognitive and emotional functions of the brain. The brain can also regulate the distribution and metabolism of the intestinal flora. The intestinal microbial imbalance of PSD patients is more different than that of normal people, which can lead to the disorder of intestinal flora through the neuroimmune pathway, which can then reduce the metabolism and synthesis of 5-HT, and aggravate the depressive state of patients. Mutant mice reduced their 5-HT levels by 60% - -80% in the CNS, that is, they showed depressive-like behavior[18], The intestinal flora can regulate the 5-HT metabolism in the body and affect the composition and function of microorganisms. Based on this judgment, 5-HT is a common node of the brain-enterobacteria axis.

With modern metagenomics and metabolomics, it is gradually clear that short-chain fatty acids (SCFAs) are one of the main metabolites of the bacterial flora[19], Including acetic acid, butyric acid, etc., can maintain the body metabolism and neuroimmune system. SCFAs can penetrate the blood-brain barrier and associate with free fatty acids to regulate neuroplasticity and gene expression, thus affecting neural function. Chronic stress and neuroinflammation play an important role in the depressive phenotype and can jointly regulate regenerative hippocampal neurons. PSD patients have increased expression of LPS synthetic genes and significantly increased plasma LPS, leading to intestinal flora dysbiosis and intestinal barrier permeability[20].

5. For PSD based on MGBA

At present, the treatment of PSD patients is mainly with antidepressants, psychotherapy and integrated Chinese and western medicine. However, long-term drug treatment will cause side effects such as drowsiness, general fatigue and gastrointestinal discomfort. Most patients are prone to repeated, poor compliance, and drug contraindications are not clearly controlled. Therefore, extensive attention should be paid to finding safe, effective and stable treatment modes with small side effects. MGBA has been widely studied in recent years, and more and more researchers are treating PSD patients by regulating intestinal microbiological balance.

The active ingredients saponin and flavonoids can inhibit apoptosis, regulate HPA axis, inhibit inflammation and improve intestinal flora, which has been confirmed in animal models[21]. Coptis tis are widely used in combination with intestinal flora to treat depressive diseases[22], Berberine significantly increased the expression of neurotransmitter expression in depressed rats, reduced NLRP 3 protein expression in rat hippocampus, effectively inhibited NOD-like receptor signaling in depressed state, and improved the inflammatory response in depression model rats.

Traditional Chinese medicine compounds or preparations are widely used in clinical practice. Modern pharmacology found that the plus and subtract to regulate the rat flora α and β diversity, reduce harmful bacteria abundance, improve the milk rod beneficial bacteria abundance and cecum metabolites, can alleviate rat depression like behavior, the polysaccharide provide rat flora nutrition, rich intestinal dominant flora abundance, increase the content of such as butyrate acid SCFAs, achieve antidepressant effect[23]. Bupleurum and liver dispersion can promote the normal level of 5-HT, NE and dopamine in rat hippocampus[24], The implantation of PSD mice could significantly increase the levels of pig cholic acid and 7-ketodeoxycholic acid in the serum of PSD mice, alleviated the depressive symptoms of mice, and increased the expression of BDNF in the hippocampus.

Intestinal flora transplantation (FMT) is a hot research topic in recent years. Through the transplantation of healthy donors, the intestinal microbial ecology of patients is reconstructed. Existing studies have proved that it is simple to operate and has few side effects. The preference and forced swimming in mice proved to improve depression-like behavior, and the serum expression level of corticosterone and

pro-inflammatory factors in the prefrontal cortex was significantly reduced; the intestinal tryptophan and brain tryptophan content in mice were intervened to relieve depression and constipation symptoms[25]。

6. Summary

To treat post-stroke depression by improving intestinal microbiota and their metabolism is a hot topic and difficult point at present. The existing studies mostly start from the pathogenesis of PSD to improve or reduce the degree of nervous system damage causing depression in the brain. By studying the overall effect of intestinal flora exerted by traditional Chinese medicine or prescription preparations, the content of intestinal beneficial and harmful bacteria can be changed, and restore the structure and metabolic level of intestinal microorganisms. It is still necessary to continue to study how traditional Chinese medicines target gut microbes and transform their active components to play biological roles. We should promote multi-target research on the mechanism of treating PSD symptoms, improve the technology of fecal bacteria transplantation and co-incubation of Traditional Chinese medicine, and repeatedly verify the personalized and precise treatment of MGBA pathway in PSD through animal tests and clinical studies.

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