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Advances in Research on Intestinal Flora and Post - Traumatic Stress Disorder

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Abstract: ***Post - traumatic stress disorder (PTSD) refers to an individual experiencing, witnessing or encountering one or more actual deaths involving himself or others, or threatened with death, or serious injury, or threatened physical integrity. Of individuals with delayed onset and persistent mental disorders. Seriously disturb the life and work of patients, and bring a heavy burden to the family and society. Intestinal flora, as a large number of microorganisms colonized in the human digestive tract, plays an important role in maintaining the physiological functions of human metabolism, immunity, and endocrine. The gut - brain axis is a two - way information regulation system that connects the brain and gastrointestinal functions. The intestinal flora can participate in the activities of the gut - brain axis under both physiological and pathological conditions, affecting brain function and certain related behaviors. Therefore, in - depth study of the interaction between intestinal microbes and PTSD, and the design of individualized drugs for the intestinal flora, can provide new research ideas and methods for the clinical prevention and treatment of PTSD.***

Keywords: post - traumatic stress disorder; gut microbiota; gut - brain axis; nervous system

1. PTSD and Intestinal Flora

Post traumatic stress disorder (PTSD) is a condition in which an individual experiences a sudden abnormal threat or catastrophic event such as an earthquake, war, or terrorist attack. Patients usually present with anxiety, fearful memory recall, and stimulus avoidance. [1 - 5] The main manifestations of PTSD are persistent recollection, persistent avoidance, and heightened alertness. ① Persistent recollection or scene memory replay: The patient involuntarily recalls the scene of the traumatic memory repeatedly. When the patient sees anything in life that can be associated with the trauma, it will cause the patient to experience the trauma here, resulting in anxiety or fear. ② Avoidance: Patients will actively avoid people and things that can trigger traumatic experiences in their lives, and refuse or resist contact with certain environments that are similar to the trauma. ③ Hypervigilance: Patients will react strongly to many details that are not noticed by normal people, and show symptoms such as irritability or irritability.

The human intestine is home to a diverse and complex community of microorganisms, dominated by bacteria. It has been shown that the intestinal flora is closely related to the development of the human body itself, the metabolism of nutrients, the normal functioning of the immune system and the development of diseases. The symbiosis of microorganisms in the human body is one of the most important conditions for the maintenance of environmental homeostasis in the human body [6]. The intestinal flora, as the largest microbial community in symbiosis with the human body, is involved in many physiological functions of the host and has received much attention in recent years. Some recent studies have found that intestinal flora can participate in the bidirectional regulation of the gut and central nervous system through neural, immune, endocrine and metabolic pathways, and that intestinal flora is closely related to PTSD. In recent years, more and more studies have reported that intestinal microorganisms are closely associated with CNS diseases such as Alzheimer's disease, Parkinson's disease, depression and multiple brain infarcts. Under both physiological and pathological conditions, gut microbes can participate in the bidirectional regulatory activities of the gut - brain axis through immune, endocrine, and vagal pathways, affecting brain function and behavior [7, 8]. Therefore, the pathogenesis and development of PTSD may have some relationship with the gut microbiota. Based on this, this paper reviews the progress of research on the correlation between gut microbiota and PTSD as follows. [9]

2. Pathogenesis of PTSD

2.1 Traditional pathogenesis

It is commonly believed that factors such as traumatic stress lead to the release of neurotransmitters and hormones. By targeting receptors acting on coupled G proteins, a second messenger is generated that triggers a phosphorylation response, which in turn downregulates downstream genes, thus causing changes in the structure and function of the corresponding cells, ultimately leading to PTSD.

Some of the more recognized pathogenic mechanisms are. ① 2017 Rapcencu, Serova et al. found dysfunctional hypothalamic - pituitary - adrenal axis (HPA) neuroendocrine regulation in patients [9 - 11]② 2016 Galesi [12] et al. found that the adrenal hormone - releasing hormone (CRF) stress system is closely related to the HPA axis. In acute post - traumatic stress or chronic stress states, sustained hypocortisol response and negative feedback inhibition of the HPA axis are enhanced [13]③ Bountress [14, 15] et al. found enhanced consolidation of patients' memories of traumatic events, patients themselves felt intense pain, and the organism's ability to integrate trauma was compromised Radley [16] et al. found that severe traumatic stress may lead to plasticity changes in the amygdala, resulting in patients Cui H [17] et al. found that the amygdala plays an important role in intrusive memory. ④ The medial prefrontal cortex (mPFC) inhibits stress behavior, and et al. found decreased function in the anterior cingulate area in patients with PTSD. Carroll [18] et al. found decreased activation of the mPFC in patients with PTSd. Williams [19] showed a negative correlation between the mPFC and the amygdala. Shin [20] et al. found that the prefrontal cortex (mPFC) modulates hippocampus - dependent memory through inhibition of the amygdala. memory.

2.2 How the flora works

Results have been used to show that in addition to the nervous system (gut - brain neuroanatomical pathway), but also through the endocrine, immune, and metabolic systems exert an influence on the brain. ① The gut microbiome - brain axis refers to the network of mutual information exchange between the two and is centered on the interaction between gut microbes and the brain [21 - 22]. There is now much evidence that gut microbes affect the brain through hormones, immunomodulators and flora metabolites [23 - 27]. ② Gut microbes have neuroendocrine effects through the neuroendocrine - HPA axis [22]. ③ The development of the intestinal immune system depends on gut microbes [28, 29]. Talham [30] et al. found that segmented filamentous bacteria in the intestine are able to restore the full function of intestinal T and B cells. ④ The intestinal flora is capable of synthesizing r - aminobutyric acid, 5 - HT, dopamine, and short - chain fatty acids, which are capable of intercellular communication [31]. ⑤ Through the intestinal mucosal barrier and the blood - brain barrier, peripherally produced inflammatory factors can directly affect the brain [32].

2.3 A link between the flora and its metabolites and traditional mechanisms

It has been reported in the literature that when serum of patients who have experienced war and developed PTSD was tested compared to normal subjects, it was found that PTSD patients had significantly higher levels of interleukin - 6 compared to healthy controls, suggesting the presence of central system inflammation in PTSD patients [33]. One possible source of inflammation in PTSD patients is the failure of intestinal barrier function, where continuous stress can increase intestinal permeability, and intestinal Increased permeability allows translocation of intestinal flora and its components (lipopolysaccharides and peptidoglycans) in the internal environment, which induces the synthesis of pro - inflammatory cytokines [34].

2.4 Brain - gut axis, intestinal influences on depression mechanisms

Gut flora is an important component of the intestinal tract and plays an important role in controlling gastrointestinal motility, promoting nutrient absorption, antagonizing pathogenic bacteria and improving immunity [35]. More and more studies are focusing on the relationship between intestinal flora and brain, and it is confirmed that there is a close information exchange between intestinal microorganisms and gut, intestine and brain, and the resulting "intestinal flora - gut - brain" axis plays an important role in brain development, mood control, depression regulation and cognitive function [36].

2.4.1 Neuroendocrine mediators

The intestinal flora is involved in the regulation of the central nervous system through the production of corresponding neurotransmitters and other neuroactive chemicals, such as intestinal chromophores, a special class of secretory cells present in the intestine that secrete the neurotransmitter pentraxin (5 - HT), and more than 90% of the body's serotonin is present in the intestine. It has been documented that pentraxin not only regulates gastrointestinal motility, but also has a significant role in mood disorders such as the regulation of depression. In addition to the direct production of neurotransmitters, gut flora can also influence brain function by regulating the way the body metabolizes related compounds. For example, gut flora can regulate the emotional activity of the brain in a paracrine manner [37] and is involved in regulating the metabolism of tryptophan, a precursor to pentraxin (5 - HT) synthesis, by influencing the production of cortisol and pro - inflammatory cytokines [38]. Similar studies have been conducted in the hypothalamic - pituitary - adrenal (HPA) axis, an important component of endocrine transmission, where the hypothalamic - pituitary - adrenal (HPA) axis regulates the release of cytokines and influences the activity of immune cells through the release of cortisol in response to external stimuli that produce stress, which affects the barrier and permeability of the intestinal tract and thus alters the structure of the intestinal flora, and conversely, the intestinal flora. In contrast, the intestinal flora can also regulate the activity of the hypothalamic - pituitary - adrenal (HPA) axis, which has an effect on the activity of the brain. It has been demonstrated that the HPA axis of germ - free mice is capable of releasing excess corticosterone and adrenocorticotropic hormone when subjected to restraint stress compared to normal group of animals, while testing germ - free mice after transplantation of normal gut flora can greatly improve the activity of the HPA axis [39]. The intestinal flora is capable of utilizing more than 30 neurotransmitters including pentraxin (5 I HT)

and dopamine (DA), but the specific role it plays locally in the gut and the mechanisms by which it affects the central nervous system are not yet clear.

2.4.2 Immune system mediators

As an important part of the "intestinal flora - gut - brain" axis, the intestinal immune system plays an important role in the regulation of the body's immunity. The immune cells present in the human intestine account for 70% - 80% of the immune cells in the whole body. [39] On the one hand, the immune system can influence the composition and diversity of intestinal microorganisms, and on the other hand, the intestinal flora can regulate the function of the immune system. [40] In addition, numerous studies have shown that gut flora affects brain function in three main ways: (i) the cytokine IL - 1 produced by gut flora in the circulatory system can bind to IL - 1 receptors produced by macrophages in peripheral blood vessels and epithelial cells in the brain to produce prostaglandin E2, thus affecting brain function and activity [41]. (ii) Gut microorganisms act on the body and induce the production of cytokines, which are transmitted to the brain through the blood - brain barrier transport system, directly acting on the brain and influencing its activity and function [42]. (iii) The specific molecular structures (MAMPs) of different intestinal flora can be recognized by Toll - like receptors (TLRs) expressed on macrophage - like cells in the periventricular apparatus and choroid plexus of the brain, producing and releasing cytokines and thus entering the brain and having an impact on its function [43]. It is known that elevated levels of cytokines are closely associated with depression - like behavior, and their levels are partially regulated by gut microbes.

2.4.3 Vagus nerve mediators

The vagus nerve transmits information between the peripheral and central nervous systems, thus constituting a direct link between the gut and the brain [44]. Many studies have shown that the neural pathway regulates the connection between the gut microbes and the central nervous system via the vagus nerve [45 - 46]. The induction of c - FOS in sensory neurons in the vagus nerve may be the mechanism of the interaction. The expression of c - FOS and the upregulation of neuronal c - FOS mRNA are generally considered as markers of neuronal activation. One study confirmed that Campylobacter jejuni, a food - borne pathogen, was able to increase c - FOS expression in vagal sensory ganglion afferent brain regions, leading to anxiety behavior in mice. In addition, the immune vagus nerve, through its terminal contacts with immune cells in the intestinal mucosa, responds to a variety of signals released by lymphocytes and mast cells, including histamine, 5 - HT and adrenocorticotropin - releasing factor (CRF) secreted by mast cells and inflammatory factors released by macrophages [47, 48]. Among them, 5 - HT is the focus of our attention because it not only has a regulatory role in intestinal motility and secretion, but also is an important neurotransmitter in emotional disorders such as depression [49]. In addition, it has been shown that probiotics can also play a role in improving behavior in mice by mediating through the vagus nerve. Conversely, after the vagus nerve is cut, probiotics such as Bifidobacterium bifidum improve colitis and the effect of anxiety behavior in mice is lost [50]. In depressed patients, the gut flora composition was significantly altered compared to controls [51 - 53], possibly due to the activation of the vagus nerve, which leads to the development of symptoms of depression.

2.4.4 Bacteriophage metabolite media

The intestinal flora regulates various metabolic reactions in the body, producing metabolites that are important for health, such as bile acids, choline and short - chain fatty acids (sCFAs); complex carbohydrates, such as dietary fiber; and short - chain fatty acids, such as n - butyrate, acetate and propionate, which are fermented in the colon by intestinal microorganisms. These fatty acids are thought to have some degree of neuroactive activity [54]. It has been shown that stools of female patients with depressive symptoms were found to contain significantly lower levels of short - chain fatty acids (e. g., acetic acid) compared to healthy women, suggesting that SCFAs may help improve depression - like symptoms [55]. Short - chain fatty acids have been reported in the literature to be shown to modulate behavior in animals. Short - chain fatty acids present in the circulatory system and not taken up by peripheral tissues are able to enter the central nervous system and subsequently cross the blood - brain barrier and enter the brain directly [56], thereby regulating the expression of genes associated with mood disorders, including CREB [57].

3. Treatment

3.1 Bacterial flora

Messaoudi M [58] et al. reported in 2011 that the use of different species of Lactobacillus and Bifidobacterium was effective in improving patients' mood, reducing the level of anxiety and relieving heart pain. A quantitative comparison of anxiety scores showed a significant decrease in the experimental group compared to the control group, and the effect was more pronounced in patients with low cortisol levels as demonstrated by experimental data. And in PTSD patients in chronic persistent stress or acute stress state, the body shows a persistent low cortisol response. Tillisch K, Labus J [59] et al in 2013 by using exogenous probiotic (FMPP) intervention in healthy volunteers for 4 weeks, FMPP include: bifidobacteria, Streptococcus thermophilus, Lactobacillus bulgaricus and Lactococcus lactis, by comparing before and after the experiment Functional magnetic resonance revealed that FMPP could affect the brain activity controlling emotion and central processing. In summary, there is an important link between intestinal flora dysbiosis and neurological and psychiatric disorders in human body. A large number of animal tests and extensive clinical trials have confirmed that direct intervention with probiotics can regulate the structure of intestinal flora in the organism, and improve the central nervous system diseases and psychiatric diseases by affecting the flora to regulate the neurological, endocrine, immune and metabolic pathways, thus alleviating the patient's condition and

improving various symptoms such as anxiety and irritability. The analysis of the changes in the intestinal flora of patients and the research of more probiotic microecological agents will become the most important work in the future, the targeted selection of probiotics to intervene in the host's intestinal flora, so that the imbalanced flora can be restored to normal, which will make the prevention and treatment of disease more effective.

3.2 Drugs

Taylor M [60] et al. in 2017 found that the use of naltrexone in combination with psychotherapy was effective in reducing symptoms in patients with PTSD.

3.3 Metabolites

Rapcencu AE [61] et al. found and reported in 2017 that cortisol arousal response is (CAR) is a well - validated standardized test in the HPA axis, and by comparing experimental and control groups, the researchers found that PTSD patients received intensive treatment while non - PTSD patients did, but CAR values slowly decreased over time in both groups, indicating that intensive psychotherapy was not significantly specific for PTSD. However, CAR values by themselves can be used as a biomarker to predict PTSD patients.

4. PTSD and Care

Nursing staff is a special and important presence in health care, always fulfilling the role of preserving life, alleviating illness and promoting health. The nature and intensity of nursing work, the population served and the stresses of daily life determine that nursing staff will face great stress and a greater chance of suffering trauma. a study by Kosydar - Bochenek J [62]et al. described the nursing profession's nature of the work and outlined the negative and positive consequences, which their experimental results point out may result from the frequent experience of traumatic events related to the execution of the work. Caregivers face more acute and chronic stressors, and a range of risk factors make caregiver PTSD and sleep disorders more common among caregivers. [63]The frequent exposure of caregivers to traumatic experiences compared to non - healthcare workers also suggests that caregivers will have a higher prevalence of PTSD. It has been documented [64]that a good sense of coherence (SOC) and a high level of resilience may reduce the risk of PTSD.

5. Prospects and Shortcomings

More and more researchers are focusing on the field of intestinal flora and its application to clinical treatment, focusing on the joint action of human body and intestinal microorganisms. The intestinal flora can participate in the central nervous system by regulating the neuroendocrine system, synthesizing various neurotransmitters and its own metabolites to form a two - way communication system to participate in many physiological processes. At present, many drugs used for the treatment of PTSD are difficult to penetrate the blood - brain barrier to reach the effective blood concentration because of the existence of the blood - brain barrier, while the intestinal flora can affect the intestine to avoid the clearance of the blood - brain barrier and achieve the therapeutic purpose by affecting the intestine and then the brain. It provides a new idea for the development of drugs for PTSD treatment. At present, the regulation of intestinal flora on the "brain - gut axis" has become a new target for neuropsychiatric diseases. A large number of studies on gut flora in neuropsychiatric disorders have been reported, and in the near future there may be new therapeutic modalities to treat PTSD by modulating gut flora. Caregivers, as a high - risk group for PTSD, should also be taken seriously in the future progress.

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