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To Explore the Brain-Gut Interaction Pathway of Intestinal Flora Based on Traditional Chinese and Western Medicine

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Abstract: There is no direct anatomical relationship between the brain and the gut, but there is a close correlation in clinical manifestations, which is called "brain-gut axis". With the breakthroughs made in the treatment of Parkinson's disease, depression, Alzheimer's disease and other fields based on the brain-gut axis theory, more and more studies have been conducted on the mechanism of brain-gut axis. The current research status mainly defines the basic concept of brain-gut axis from the perspective of traditional Chinese and western medicine, expounds and analyzes the related mechanism and modern clinical application of brain-gut axis. Therefore, the following review summarizes the understanding and research progress of "brain-gut axis".

Keywords: Brain-Gut Axis; Gut Microbiota; Mechanism of Action; Traditional Chinese and Western Medicine Dimensions

Introduction

The brain-gut axis (brain-gut axis) is the bidirectional communication between the enteric nervous system (ENS) and the central nervous system (CNS). In recent years, scientific studies have pointed out that intestinal dysfunction can increase the risk of central nervous system diseases, such as neurodegenerative diseases and other mental diseases. The small intestine can not only influence brain activity by using microbiota, but also interact with the human brain through the nervous system, immune and endocrine pathways of the "brain-gut axis". The close relationship between them has gradually attracted people's attention. This article reviews the interaction pathways between the gut and the brain, mainly based on intestinal flora, so as to provide reference for revealing the nature of the "brain-gut axis".

1. Understanding of brain-gut axis in western medicine

The brain-gut axis is composed of brain, gut and intestinal microorganisms, and is jointly participated by the central neuroendocrine system, enteric nervous system, autonomic nervous system and hypothalamic-pituitary-adrenal axis system [1]. The central nervous system modulates the signals of the brain-gut axis and transmits them down to the gastrointestinal tract to express their functions, while the enteric nervous system can regulate the brain-gut interaction through this bidirectional regulation process, also known as brain-gut interaction [2].

2. Explore the brain-gut interaction pathway based on intestinal flora from the perspective of western medicine

An important part that makes up the brain-gut axis is the content of gut bacteria. Relevant literature reports that brain-gut interaction is involved in the pathogenesis of Parkinson's disease, depression, Alzheimer's disease and other diseases [3-5], most of which are accompanied by precursors such as intestinal flora imbalance, digestive system diseases, and brain-gut axis dysfunction. Moreover, studies have shown that intestinal flora may affect neurogenesis [6] and myelination [7], the normal function of hypothalamic-pituitary-adrenal cortex and endocrine system [8], and intestinal flora has a certain maintenance effect on the formation of blood-brain barrier and can promote the maturation of immune system [9]. Intestinal flora is mainly responsible for regulating the physiological, behavioral and cognitive functions of the brain It is accomplished by neural, endocrine and immune pathways.

2.1 Regulation of gut microbiota-neuroendocrine pathways

The hypothalamic-pituitary-adrenal axis jointly affects the brain, gastrointestinal nervous system and endocrine system [10]. The signal transmission of the stress sympathetic nerve to the enteric nervous system is the main path for the axis to directly affect various functions

in the stomach. Intestinal flora also has a huge negative impact on various sensory and endocrine functions in the stomach. Similarly,when gastrointestinal absorption function is disturbed, gastrointestinal inflammatory factors and gastrointestinal bacteria act on the axis, which will also affect the cognitive and behavioral functions of the brain.

2.1.1 Gut microbiota-nervous system interaction

Gut microbiota can affect the production of neurotransmitters by regulating the function of intestinal epithelial cells or directly synthesizing and secreting GABA, 5-HT, Na, dopamine and other neurotransmitters. Studies have found that gut microbiota can play a role in the central nervous system and is closely related to 5-HT, with bilateral effects [11]. 5-HT is stimulated and regulated by abundant specific intestinal flora and metabolites, binds to receptors, and participates in hypothalamic-pituitary-adrenal regulation under the action of various receptor subtypes, stimulating the secretion of adrenocorticotropic hormone (ACTH), cortisol and other axis regulating hormones. If the gut microbiota is dysregulated, neurotransmitters enter the HPA axis through the peripheral blood vessels, bind to 5-cranial nerves and receptors, and interfere with cortisol and CRH secretion, attenuate the activity of 5-HT neurons, leading to complete axis disorder and brain abnormalities. In addition, some scientists have studied that brain-produced neurotrophic factors can affect neuronal activation [12], and when intestinal flora changes in infectious disease models, it will change the expression of certain proteins, which will have an impact on the increase in anxiety [13].

2.1.2 Interaction between gut microbiota and endocrine system

Intestinal flora can control intestinal endocrine cells to produce adrenocorticotropic hormone releasing factor (CRF), adrenocorticotropic hormone (ACTH), adrenocortical corticosterone (CORT) and other hormones, activate the function of HPA axis [14], and release Glucocorticoid (GC), which is involved in the growth of neurons , differentiation and apoptosis, can regulate the state of neurons and glial cells, and then affect the plasticity of neurons, leading to the functional changes of the central nervous system [15]. Similarly, the composition of gut microbiota is regulated by the stress response and the HPA axis [16]. Several studies have suggested that the activation of the HPA system and the release of CRF and GC may protect the gastrointestinal mucosa during chronic stress [17].

2.2 Intestinal microbiota-Immune regulation

The combination of host and cells develops for a long time to form a relatively balanced environment of the digestive tract microbiome, which participates in important biological processes including host metabolites, nutrient products and immunity, especially plays a crucial role in the construction and improvement of the host immune system. Relevant studies have confirmed that the intestinal flora in the host directly or indirectly affects the host immune system [18], and the intestinal flora promotes the development of the immune system and also affects the differentiation process of immune cells. The immune pathway is also one of the ways to connect the gastrointestinal tract and the brain through the bidirectional interaction of the brain-gut axis.

2.2.1 Intestinal barrier interaction

The gastrointestinal barrier composed of the intestinal mucosa plays a crucial role in the brain-gut axis pathway. Disruption of the integrity of the intestinal mucosal barrier can easily cause inflammation and affect intestinal motility, sensation and hormone secretion [19]. This is because the destruction of the intestinal mucosal barrier will make the molecular structure bound to the intestinal mucosal surface release immunoactive substances such as proteases, and produce some inflammatory cytokines that pass through the intestinal mucosal barrier. The intestinal epithelial barrier is closely related to the homeostasis of the internal environment [20]. The entry of macromolecules and microorganisms into the gut and lymphoid tissues is controlled by microbiotic cells in the intestinal epithelial barrier. The outer layer of mucus is tightly distributed with a dynamic barrier composed of glycoproteins called biofilm. This glycoprotein biofilm is broken down by microorganisms during low dietary fiber and increases sensitivity to pathogen recognition.

2.2.2 Blood-brain barrier interaction

The diffusion barrier between the central nervous system and the cerebrospinal fluid is usually formed by clathrin [21], which builds up the endothelial cells of the cerebral blood vessel wall. Permeability to this barrier, in turn, is determined by organic factors released by the intestinal bacterial population that control connexin expression. Recent studies have shown that an important signal metabolite affecting the blood-brain barrier may be short-chain unsaturated fatty acids [22]. Short-chain unsaturated fatty acids act on the blood-brain barrier through

genetic modification. Microglia, the immune cells in the central nervous system, can be activated by intestinal microbes to release immune factors that regulate the function of the nervous system, thereby affecting the physiological activities of the brain.

3. Understanding of brain-gut axis in traditional Chinese medicine

In traditional Chinese medicine, the role of "brain" in the brain-gut axis is interpreted as the regulation of cerebrovascular diseases and emotional disorders, and the regulation of "intestinal tract" can be interpreted as the regulation of visceral function related to digestion. The term "brain-gut axis" is not mentioned in traditional Chinese medicine, but modern medicine has confirmed that the brain-gut axis is closely related to the spleen, liver and kidney [23-25]. The normal life activities of the human body depend on the five zang organs, and the brain, as the original spirit, dominates the spiritual consciousness and sensory movement of the whole body. At the same time, the meridian system connects the five zang organs, qi and blood, Yin and Yang of the human body, and its circulation and syndromes are also closely related to the brain.

3.1 Integration of heart and brain sensing

The theory of traditional Chinese medicine believes that the generation of emotion originates from the brain and originates from the heart, and gradually forms the concept of "the heart and brain induction integration". People often say "using the brain" as "heart". "Suwen-Linglan Secret classic" says: "The heart, the official of the monarch, God out of the Yan". The Medical Classic Jingyi says, "All things enter the brain through the eye, through the ear, and through the heart." Zhang Xichun's Yi Xue Zhong zhong shen Xilu (Medical Zhongzhongshen Xilu) of the Qing Dynasty wrote, "The human deity is originally located in the heart and the brain, and the function of the deity is supplemented by the heart and the brain. The brain for the original god, the heart for the god.If a man wants to use his God, he will reach his heart from his head. If he does not use his god, he will return from his heart to his head." Referring to the textbook Basic Theory of Traditional Chinese Medicine, the functions of heart and brain are described as "heart governs mind" and "brain assists heart in regulating human spirit, consciousness, thinking, and functional activities of zangfu organs." It can be seen that ancient and modern doctors generally believe that the brain and heart are connected and perceive external things together.

3.2 Heart-gut relationship

The theory of "the exterior and interior of the heart and the small intestine" was first put forward in the Benshu (Shu of Miraculous Pivot), "the heart connects the small intestine". From the theory of meridians, in the book Meridians of Miraculous Pivot, it is written: "The heart and hand are shaoyin vessels, which originate from the heart, originate from the heart system, and are lower than the diaphragm and small intestine". The relationship between the heart and the small intestine can also be reflected from the physiological function. For example, Zhu bing Yuan hou Lun (Theory of All Diseases, Sources and Syndromes) believes that the small intestine has the function of helping the heart to discharge water. "The heart of the small intestine is also, its water and qi descending to the small intestine is the Ao stool, then the heart has no stop drinking, and the body fluid and water drink stop accumulation, forced by the heart, so that the heart is not smooth, so the pain and more saliva also"; According to the pathological manifestations, the heart fire is transferred to the small intestine, and the water is injected into the bladder through the three jiao, causing difficulty in urination. And the small intestine has heat can also follow the meridian inflammation in the heart, visible upset, tongue red erosion and so on. Therefore, the heart and small intestine are exteriors and exteriors of each other, and cooperate, influence and connect with each other in physiology, pathology and meridians.

4. Explore the brain-gut interaction pathway based on intestinal flora from the perspective of traditional Chinese medicine

It has been found that the balance of Yin and Yang in the internal environment system of the body is determined by the circulation movement mechanism of "Qi ascending and descending" of the whole body function of the viscera, and the functional ascending and descending and constitutive mechanism are determined by the characteristics of qi ascending and descending of the corresponding viscera, re-

spectively. Under the support of the theory of brain-gut axis, the combination of spleen, liver and kidney is the main cause and pathogenesis of the human body, and the three can also interact.

4.1 Qi of spleen and stomach and Yin-Yang-intestinal flora

As the driving force of the brain-gut axis system, gut microbiota is involved in the regulation of brain-gut axis pathways. The imbalance of intestinal flora will affect the balance of the internal environment, such as the normal physiological function of the digestive, nervous, endocrine and immune systems, thus affecting the overall function [26]. Yin and Yang change with the rise and fall of middle qi, which is the qi of the spleen and stomach, and the rise and fall of middle qi is the driving force for the growth and change of all things. Through qi, blood, meridian-collateral and other systemic auxiliary substances, its imbalance will also affect the dysfunction of the whole body. There is no term "gut microbiota" in traditional Chinese medicine. Therefore, in traditional Chinese medicine, the intestinal flora can be understood as the qi of the spleen and stomach and the Yin and Yang of the spleen and stomach. Maintaining the homeostasis between probiotics and pathogens in the gut microbiota plays a key role in the proper functioning of the body. Under physiological conditions, maintaining a stable intestinal microecology is an important part of the normal rise and fall and smooth circulation of human qi, which can mainly reflect the function of the spleen and stomach.

4.1.1 Brain, spleen and intestine related

The relationship between the spleen and stomach and the brain is extremely close, and there is a relationship between meridian-qi and substance. The meridian system is an important bridge of the brain-gut axis in traditional Chinese medicine. The stomach meridian runs into the brain in foot-yangming, and the stomach and brain meridian are connected by qi. In the Wu Long Jin Ye bie of Miraculous Pivot, it says, "When the body fluids of the five grains are combined and become an ointment, they penetrate into the bone cavity and replenish the brain." The blood and essence of the spleen and stomach nourishments the normal physiological function of the brain, and the transport of blood and semen depends on the promotion of the spleen and stomach qi. On the one hand, the imbalance of Yin and Yang of spleen and stomach qi can lead to insufficient brain bone marrow and insufficient qi and blood, which affects brain function. On the other hand, the brain has the role of dominating life activities and directing whole body functions. If the perception ability of the brain decreases, the brain loses contact with the spleen and stomach, and the spleen and stomach cannot receive and transport normally, followed by abdominal distension, diarrhea, poor stool and other digestive problems. If the brain is damaged, it will damage the spirit and cannot drive the reception and transportation of the spleen and stomach, resulting in the loss of the movement function of the spleen and stomach, abnormal rise and fall of qi, insufficient blood gas and biochemistry, damage to the function of the main spleen muscles and limbs, muscle weakness, fatigue and other symptoms. [27]

4.1.2 Liver, spleen and brain related

Traditional Chinese medicine proposes that the liver plays a key role in the relationship between the rise and fall of the spleen and stomach. Liver-qi disharmony inevitably affects the laxative function of the liver. Liver against spleen and stomach, resulting in loss of temperament, qi stagnation, qi and blood discord. The body temperature is low, qi and blood are insufficient, and the stomach can not eat, which aggravates the lack of liver blood and stagnation of liver qi, resulting in the loss of mental nutrition. In addition, TCM proposes that the normal functions of spleen, stomach and consciousness are closely related to the unobstructed liver. According to the Miraculous Pivot: Meridian, "The vessel of liver foot Jueyin reaches the lower abdomen, clamp the stomach and leaves the forehead, and meets the governor vessel at the top." It can be seen that the liver meridian runs down to the gastrointestinal tract and up to the top of the roof, which is an indispensable channel for brain-gut communication. The brain also has the function of regulating emotions and splenic anxiety. Lack of spirit, excessive use of the brain, mental stress or depression, it is easy to cause spleen deficiency. Lu Dianqiang et al. [28] believed that the normal rise of middle coke can ensure normal emotional activity. Spleen blood, blood and heart; Spleen dysfunction, mental and nutritional deficiencies, and mood disorders are the result of the absence of the spirit in the spleen

4.1.3 Spleen, kidney and brain related

Huangdi Neijing (Yellow Emperor's Internal Classic) once put forward the theory that "the kidney hides the essence and the essence generates the marrow", which means that the brain bone marrow is produced by the congenital kidney essence. The governor vessel and the

bladder meridian form the channel between the kidney and the brain. From a physiological point of view, the spleen meridian and the governor vessel are connected between the mouth and the heart, and Yang qi should be injected into the governor vessel by the stomach meridian. The governor vessel regulates the Yang qi of the whole body, circulates along the meridians and the brain, and strengthens the connection between the spleen, stomach, the governor vessel and the brain. The meridians of the spleen are connected to those of the bladder, which pass through the abundant muscles on both sides of the spine. Thus, it depends on the function of the splenic innervating muscles and the spleen and stomach as the basis for acquiring acquired postnatal. In terms of pathology, the kidney loses its shuttering function, the kidney Yin cannot converge, the kidney Yang and spleen Yang cannot be attributed to the kidney house, the kidney Yang is deficient, the promotion is weak, the evaporation and gasification function is lost, and the water metabolism is abnormal. Kidney water insults spleen soil, conditioning weakness, aggravation of systemic gasification dysfunction [29]. Based on the above discussion, the brain-gut axis pathway in modern medicine can be generally understood as the relationship between spleen, brain and intestine in traditional Chinese medicine.

5. Summary and Prospect

In the 21st century, the pace of life is getting faster and faster, science and technology and medicine are developing rapidly, but we still face many medical problems. Brain-gut axis is a turning point for human beings to understand and break through the difficult problems of mental or gastrointestinal diseases. Modern scientific research [30] points out that gut microbiota can affect individuals to improve brain and gut functions through the microbiota-gut-brain axis. The heart and small intestine are the outer and inner parts of each other, mainly reflecting the function of helping the small intestine digest food. Learning from the perspective of the heart is from the perspective of the brain. Based on this, under the framework of the disease treatment function of modern clinical traditional Chinese medicine and western medicine combined with the theoretical basis of internal correlation in clinical research, this paper systematically and in detail discusses the mechanism of disease regulation by the bacteria-brain-gut axis, analyzes and construct the relationship between neuropsychiatric diseases and gastrointestinal diseases from multiple angles, and provides new ideas for the development of related drugs and the treatment plan of coupling diseases of nerves and gastrointestinal Road. At present, in view of the fact that there is no unified understanding of the mechanism and prognosis of brain-gut axis system in regulating gastrointestinal diseases among many domestic and foreign basic researchers and scholars, many researches are focused on the basic problems of dynamic monitoring and management of intestinal flora balance function. The future research direction should focus on exploring the biological dynamic mechanisms of the brain-brain-gut axis system in the cooperative regulation of brain-gut diseases and the development of brain-gut diseases, and expounds the various biological mechanisms of how the body automatically realizes the simultaneous treatment and regulation of stomach, brain, and gut functions.

References

[1] Wang LD, Du XJ, Liu JH, et al. Research ideas of soothing the liver and strengthening the spleen in the treatment of functional dyspepsia based on brain-gut interaction [J]. Chinese Medicine Research,2019,32(04):1-3.

[2] Howard R Mertz. Overview of functional gastrointestinal disorders: dysfunction of the brain-gut axis[J]. Gastroenterology Clinics of North America,2003,32(2).

[3] Liu LJ. Study on the correlation between constipation and depression in Parkinson's disease based on the theory of "brain-gut axis" [D]. Anhui University of Traditional Chinese Medicine, 2017.

[4] Qu Y, Hu JQ, Wu S, Wang CC, Rong Fei. Treatment of Alzheimer's disease with spleen based on the theory of brain-gut axis [J/OL]. World Traditional Chinese Medicine:1-9[2022-07-10].

[5] Xiang YY, Shi HY, Tan AH, Xie GJ, Ran SM, Wang P. Treatment of vascular dementia with brain and intestine in traditional Chinese medicine based on the theory of "brain-gut axis" [J]. Shizhen Traditional Chinese Medicine and Chinese Medicine, 2021, 32(09): 2231-2233.

[6] Ogbonnaya ES, Clarke G, Shanahan F, Dinan TG, Cryan JF, O'Leary OF. Adult Hippocampal Neurogenesis Is Regulated by the Microbiome. Biol Psychiatry. 2015 Aug 15;78(4):e7-9.

[7] Hoban, A., Stilling, R., Ryan, F. et al. Regulation of prefrontal cortex myelination by the microbiota. Transl Psychiatry 6, e774 (2016).

[8] Sudo N. Microbiome, HPA axis and production of endocrine hormones in the gut. Adv Exp Med Biol. 2014;817:177-94.

[9] Honda, K., Littman, D. The microbiota in adaptive immune homeostasis and disease. Nature 535, 75–84 (2016).

[10] Bonaz BL, Bernstein CN. Brian - gut interaction in inflammatory bowl diseases [J]. Gastroenterology, 2013144 (1).

[11] Ning HJ. Research progress on the relationship between intestinal microecology and digestive system diseases [J]. Chinese Medicine Guide, 2019, 17(19):17-19.

[12] Zhan TY, Cai ZL. Research progress of acupuncture and moxibustion regulating neuroendocrine function in chronic fatigue syndrome [J]. Jiangxi Traditional Chinese Medicine, 2012, 53(01): 68-72.

[13] Mary Bates. Gut Feeling: Researchers Are Discovering a Link Between Depression and Gut Bacteria[J]. IEEE Pulse, 2017,8(6).

[14] Liu RT. The microbiome as a novel paradigm in studying stress and mental health.[J]. The American Psychologist, 2017 regulation (7).

[15] Lyte M. Microbial endocrinology in the microbiome-gut-brain axis: how bacterial production and utilization of neurochemicals influence behavior[J]. PLoS pathogens, 2013, 9(11).

[16] Javad Barouei, Mahta Moussavi, Deborah M Hodgson. Effect of maternal probiotic intervention on HPA axis, immunity and gut microbiota in a rat model of irritable bowel syndrome[J]. PLoS ONE, 2017,7(10).

[17] Kieran Rea, Timothy GD, John F. Cryan. The microbiome: A key regulator of stress and neuroinflammation[J]. Neurobiology of Stress,2016,4(C).

[18] Zhao YF, Qu HB. Effect of enteral microecological nutrition support on platelet parameters, intestinal flora and immune system function in children with ITP [J]. General Nursing, 2021,20(24):3404-3406.

[19] Qin, J., Li, R., Raes, J. et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65 (2010).

[20] Li YC, Wang CF, Yang GL. Animal gastrointestinal epithelial barrier role in the stable control of intestinal environment [J]. Chinese journal of veterinary, 2015, 35 (6): 1031-1036.

[21] Jiang S. Dyrk1a regulates LAG3 gene methylation in the pathogenesis of Parkinson's disease [D]. Xinjiang medical university, 2021.

[22] Carlezon WA Jr, Mague SD, Parow AM, Stoll AL, Cohen BM, Renshaw PF. Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. Biol Psychiatry. 2005 Feb 15;57(4):343-50.

[23] Feng WL, Wu HT. A study on the pathogenesis of irritable bowel syndrome from "porta purpura is also the causative agent of five zang organs" [J]. China Journal of Basic Medicine of Traditional Chinese Medicine,2016,22(10):1314-1316.

[24] Lin XY, Cai GX, Tan YS. Discussion on the theory of "spleen and kidney correlation" from the brain-gut axis [J]. Shizhen Medical Sinopharm, 2015,26 (9): 2210-2211.

[25] Tran N, Zhebrak M, Yacoub C, Pelletier J, Hawley D. The gut-brain relationship: Investigating the effect of multispecies probiotics on anxiety in a randomized placebo-controlled trial of healthy young adults. J Affect Disord. 2019 Jun 1;252:271-277.

[26] Quigley EMM. Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. Curr Neurol Neurosci Rep. 2017 Oct 17;17(12):94.

[27] Sudo N. Microbiome, HPA axis and production of endocrine hormones in the gut. Adv Exp Med Biol. 2014;817:177-94.

[28] Wei XM, Liao L, Hu ZP, Xie CG. Analysis of blood glucose fluctuation in diabetes mellitus from the theory of "One breath flow" [J]. Chinese Journal of Traditional Chinese Medicine,2020,61(16):1463-1465. (in Chinese)

[29] Huang XQ, Liao XP. Research progress on the correlation between gut microbiota and depression [J]. Chinese Journal of Applied Neurology, 2019,22 (1): 112-116.