

# Discussion on the treatment of children's mental retardation from heart and spleen based on brain gut axis theory

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**Abstract:** The theory of brain gut axis provides a new idea for the clinical treatment of brain gut related diseases. The incidence rate of children with mental retardation has been increasing year by year, and it has become a key problem that affects children's growth and development urgently. As a new research target, brain gut axis theory has an inseparable connection with this disease. Therefore, this paper aims to explore the relationship between the theory of brain gut axis and the treatment of children's mental retardation from the heart and spleen in traditional Chinese medicine, it also explores the scientific connotation of traditional medicine and modern medicine, in order to provide a new perspective for the clinical treatment of children with mental retardation.

**Keywords:** Brain gut axis, Mental retardation, Heart spleen-brain gut, Neurotransmitter, Brain gut peptide, Intestinal flora, Immune system

## 1. Introduction

Intellectual development disorder (IDD), also known as mental retardation, mental retardation, etc., occurs in the developmental stage, including the defects of intelligence and adaptive function, which are manifested in the fields of concept, social and Only the common deficiency of IQ and SAB can be diagnosed. Clinically, it can be manifested as speech, cognitive, developmental delay, attention disorder and so on [1]. According to reports, the prevalence of IDD in children is 1%-2%, and the total prevalence rate is 1.20% in China. The incidence rate is increasing gradually [2], which seriously endangers children's growth and development, brings great burden to families and society. Nowadays, the treatment methods for children with IDD are increasing day by day, and traditional medicine also occupies an important position in the treatment. Among them, regulating and tonifying the heart and spleen is one of the important principles in the treatment of IDD. By regulating and tonifying the heart and spleen to nourish the heart and spleen, enlightening and enlightening, the spleen can be active, the heart blood can be replenished, the heart pulse can be nourished, and the essence and blood can be generated to nourish the brain. In recent years, the discovery of brain gut axis provides a modern research basis for the treatment of IDD in children by regulating heart and spleen. The treatment of IDD based on heart and spleen is widely recognized by the medical community. Therefore, based on the theory of brain gut axis, the author discusses the treatment of children's mental retardation from the heart and spleen, in order to provide the basis for modern clinical application of traditional Chinese medicine.

## 2. Theory of heart spleen brain intestine communication

The intestine of Western medicine corresponds to the spleen, stomach, small intestine and large intestine of traditional Chinese medicine, and the brain of Western medicine corresponds to the heart and brain of traditional Chinese medicine. The theory of brain gut axis in western medicine is similar to the theory of exterior interior of heart and small intestine in traditional Chinese medicine, which indicates that there are also theories similar to brain gut axis in the theoretical system of traditional Chinese medicine [3]. "Su Wen · Yin Yang Ying Xiang Da Lun" says: "Heart produces blood, blood produces spleen." "Lingshu · meridians" also says: "the pulse of spleen and foot Taiyin... Its branches are from the stomach, don't go up to the diaphragm, and focus on the heart." It is clearly proposed that the heart and

spleen meridians are connected. The heart is the master of emotion, and can generate emotion according to the situation; The spleen is the pivot of emotion, and thinking in the heart makes the spleen respond. The heart is related to the spleen, mother and son. People's thinking comes from the heart, should be in the spleen. Excessive thinking leads to qi stagnation, and should be in the spleen, which leads to the loss of Qi. The material basis of emotional activity is Qi and blood produced by Zhongjiao. The normal progress of emotional activity depends on the rise and fall of Qi mechanism of Zhongjiao. If the spleen is not healthy, dampness is endogenous, Qi and blood are lack of biochemical source, and the mind is lack of nourishment, emotional disorder will occur [4]. The essence of water and grain of spleen transportation depends on the function of heart governing blood vessels to convert red blood from heart, and also depends on the warmth of heart Yang and the promotion of heart qi to run the whole body. If the heart qi and heart Yang are insufficient, the heart vessels are dystrophic, the mother's disease and the son's disease lead to the disorder of spleen transportation, the gastrointestinal diseases such as poor food intake will appear. The rotten food of the stomach is transported by the spleen and turned into fine and dross, which is absorbed by the small intestine and transported by the spleen to nourish the whole body. The dross is transmitted by the large intestine, and its transmission function needs the assistance of the spleen. Therefore, the transformation of shuigu is the result of the synergy of spleen, stomach, intestines and intestines, and the function of intestines and intestines needs the help of spleen. If the spleen and stomach are damaged, the spleen transportation is not healthy, the small intestine secretion is out of balance, and the large intestine conduction is out of balance, the symptoms such as diarrhea and constipation can be seen; According to the traditional Chinese medicine, the brain is "the house of Yuan Shen" and the heart is "the official of the monarch". The heart and brain are in charge of the deities, the activities of human consciousness and the functions of viscera. "Lingshu meridians" says: "the pulse of Shaoyin in the heart and hands starts from the heart... Collaterals of small intestine", which indicates that the heart and small intestine are the exterior and interior of each other, and food depends on the digestion and absorption of the gastrointestinal tract, which is consistent with the theory that the spleen governs transportation and transformation. Therefore, the theory of heart spleen brain intestine communication has guiding significance in clinical application.

### 3. Brain gut axis and theoretical basis of treating IDD from heart and spleen

In the diagnosis of diseases, traditional Chinese medicine emphasizes on the whole, and the five zang organs and six Fu organs are connected with each other. Guided by the basic theory of traditional Chinese medicine, the treatment of diseases is not a certain treatment for a certain disease, but more emphasis on the dialectical treatment of the whole. Based on the theory of brain and intestine from heart and spleen, it is not only suitable for brain diseases, but also for the treatment of other diseases. The theory of heart and spleen has been applied to digestive system, nervous system, cardiovascular system, anemia, tongue disease and other diseases, and this diagnosis and treatment idea has been developed to a certain extent [5].

Traditional medicine has not yet recorded the term "mental retardation", but according to its symptoms, it can be classified into "five late five soft" category. IDD is located in the brain and is closely related to the heart, spleen, liver and kidney. Most of them are based on congenital body deficiency, with phlegm and blood stasis as the standard. Deficiency of both heart and spleen is the common cause. The heart governs the gods and blood vessels, and is filled with brain to generate marrow. If the heart is insufficient, there is no way to generate marrow. It can be seen that the gods are out of nourishment, the brain is not full, the growth is slow, and the intelligence is low. The spleen and stomach are the biochemical sources of Qi and blood. If the spleen and stomach are deficient, it will lead to the weakness of Qi and blood, the loss of heart and blood, the restlessness of mind and the insufficiency of essence, which will lead to the absence of mind and the disorder of growth and development. The heart and spleen are mother and son, and they are complementary. If the heart fire is deficient and can't nourish the spleen, or the spleen and stomach are weak and can't nourish the heart, it is easy to form the syndrome of deficiency of heart and spleen, and it is easy to cause children's mental retardation. The spleen belongs to the viscera, and the brain is listed as a Qi Heng Fu organ. It looks like a fu organ and works as a viscera. It mainly stores marrow but does not diarrhea. Although it has different properties, it interacts with each other. The spleen provides the material basis for the physiological activities of the brain, while the brain can regulate the function of the spleen. The theory of brain gut axis provides evidence for the interaction between the brain and the spleen and stomach. According to "Yishu Zazheng Huishen" spleen and stomach all have Spleen Qi". Brain gut peptide, an important substance in brain gut axis, can be regarded as a part of acquired essence, and it depends on the transfer function of spleen to distribute to different parts with the rise and fall of Qi. In addition, the heart and brain regulate the mental activities of the

human body, which can confirm the correlation between the brain gut axis theory and the treatment of IDD from the heart and spleen.

#### **4. Modern research mechanism**

##### **4.1 Brain gut axis**

It was thought that the gastrointestinal tract was a passive organ controlled by the central nervous system until it was found that it had an independent intestinal nervous system. The enteric nervous system monitors the whole digestive tract, and does not need to get instructions from the central nervous system, but operates independently. It has dual functions of afferent and efferent. Some scholars also named the intestine as the "second brain" of the human body. Medical scientists have gradually realized that the brain and intestine interact with each other through a variety of ways, which is called brain gut axis. Brain gut axis is composed of brain, gut and gut microorganisms. It controls the functions of brain and gut through visceral stimulation, nerve conduction, brain gut peptide, neuroendocrine immune regulation and other pathways. It is a two-way communication pathway that connects cognitive and emotional center with neuroendocrine, intestinal nervous system and immune system [6]. Human thinking and emotion affect the gastrointestinal tract. The brain receives stimulation and transmits signals to the gastrointestinal tract through the central nervous system, spinal cord, autonomic nerve and intestinal nerve, producing a series of gastrointestinal reactions. At the same time, visceral activities also act on the central nervous system. Gut brain axis and its regulation by microbiota may play a key role in neurodevelopment, age-related and neurodegenerative diseases. Vagus nerve, as the link between gut and brain, can transmit intestinal flora signals to brain quickly. Some experiments have shown that vagus nerve afferent response to a variety of stimuli, including cytokines, nutrients, intestinal peptides and hormones [7].

##### **4.2 Neurotransmitters and IDD**

The gut and brain are also linked by neurotransmitters, which control our emotions. For example, 5-hydroxytryptamine (serotonin, 5-HT) is a factor of perceived pleasure, which is very important for people's emotional regulation. Intestinal flora plays an important role in the production of neurotransmitters. Intestinal microorganisms can affect serotonergic, GABAergic, noradrenergic and dopaminergic. The results showed that the concentrations of aromatic amino acids in the large intestine, blood and hypothalamus decreased after antibiotic infusion, while the concentrations of serotonin and dopamine in hypothalamus decreased; After corn starch infusion, the concentration of aromatic amino acids in the large intestine, blood and hypothalamus increased, accompanied by the increase of hypothalamic 5-hydroxytryptamine and dopamine, indicating that the expression of neurotransmitters in the brain of the host may be regulated by the microorganisms in the large intestine [8]. Dopamine (DA) is considered to be the main regulator of cognitive function. The brain gut axis is the key to the physiology and pathology of neuropsychiatric diseases, which involve the impairment of dopaminergic neurotransmission [9]. Antipsychotics with DA receptor blocking effect can reduce hyperactivity, stereotype and irritability in children. Therefore, it is speculated that the enhancement of DA function may be related to the occurrence of IDD in children, but this is only a case, which needs further study. Clinical examination showed that some IDD children's blood 5-HT level increased, 5-HT synthesis in cortex and thalamus decreased, 5-HT precursor tryptophan deficiency can aggravate the symptoms of children, low maternal 5-HT level may affect fetal brain development, and become one of the risk factors of children's language retardation and mental retardation.

##### **4.3 Brain gut peptide and IDD**

The discovery of brain gut peptides provides a solid foundation for the establishment of brain gut axis theory. Brain gut peptides include but are not limited to substance P. The discovery of substance P in gastrointestinal tract denies the theory that brain gut peptides only exist in brain tissue. Brain gut peptides are considered to be the material basis of gut brain interaction. Brain gut peptide secreted by brain gut interaction plays an important role in regulating gastrointestinal and some systemic changes. Some scholars believe that the essence is the main content of brain gut peptide, which through the channels of meridians and collaterals, up and down with the Qi, disperses the viscera and organs, and plays the physiological function of human body [10]. Modern medicine shows that peptide secreting cells in the gastrointestinal tract and brain are derived from the neuroectoderm. Brain gut peptide participates in many reactions in the body through its two-way regulation of brain and gastrointestinal tract. The

secretion of brain gut peptide is often abnormal in the state of stress and emotional stimulation, which can lead to gastrointestinal dysfunction or visceral hypersensitivity. The secretion of brain gut peptide is also affected by the intestinal flora. Brain gut peptide is the target hormone involved in the brain gut axis, which can directly act on the brain to regulate emotion, stress recovery and gastrointestinal movement [11].

#### **4.4 Intestinal flora and IDD**

Intestinal flora is an important part in the regulation of brain gut axis. Its functions include digestion, absorption, immunity and nervous system development [12]. The disturbance of intestinal microflora can cause changes in host behavior, which may directly affect the central nervous system by activating neurons in the stress system. The colonization of microorganisms in the gut during the fetal period can affect the development of the brain, and has a lifelong impact on the human body. Early intestinal microflora is also very important in shaping health. People's emotions can affect the composition of intestinal flora, and some intestinal microorganisms may also affect people's emotions. The communication pathways between the microbiota and the brain include vagus nerve, gut hormones, immune system, tryptophan metabolism or microbial metabolites [13]. The maintenance of intestinal microecological stability is closely related to the growth and development of human body. It can not only promote digestion and absorption, supply energy, maintain immune barrier and enhance immune function, but also regulate the balance of energy metabolism and maintain the homeostasis of internal environment. Studies have shown that there is a dynamic balance between the diversity of intestinal microbial system and health status. Microorganisms entering the human body will be regarded as immune antigens. Pathogenic microorganisms can be recognized and cleared by the human body through immune response. The diversity of microbial flora is positively correlated with immune level. Microbial flora helps to maintain a variety of body functions, such as promoting intestinal peristalsis, regulating a variety of functional metabolism, promoting intestinal motility immune response [14]. Intestinal microorganisms can also affect the nervous system through the hypothalamus pituitary adrenal (HPA) axis. Hosts with different intestinal microflora have different reactions through the HPA axis. The loss of intestinal barrier will lead to changes in the HPA axis, damage the hippocampal precursor cells, reduce the expression of brain-derived neurotrophic factor or protein in the hippocampus, and lead to anxiety, mental retardation and other diseases [15].

Forsberg H [16] found that microbiome plays an important role in brain function, and the destruction of microbiome may be related to the etiology of neurodevelopmental disorders. Fr ö Hlich et al. [17] found that the decline of the number and diversity of intestinal microflora was accompanied by the decline of learning and memory, as well as the decrease of exploratory behavior. The development of fecal bacteria transplantation technology further revealed the relationship between the changes of intestinal microflora and nervous system dysfunction. Many literatures have reported the role of intestinal flora in maintaining the normal physiological function of the host. The destruction of the balance of intestinal flora will lead to changes in brain function, emotional changes and cognitive impairment of the host [18]. Clinical studies have shown that different bacterial metabolites have potential positive and side effects in brain diseases, including changes in catecholamines caused by immune regulation and histone deacetylase inhibition, and anti-inflammatory effects caused by aryl hydrocarbon receptor activity. This discovery highlights the changes of bacterial metabolites in patients with various brain diseases, as well as intestinal derived SCFA, SCP-cresol, indole derivatives and bacterial amyloid may affect the development and progression of the disease [19]. It is worth noting that in the intestinal pathological process of increased permeability of intestinal barrier, the translocation of bacterial products can increase the production of cytokines and affect the blood-brain barrier, and various inflammatory factors can transmit inflammatory signals to the central nervous system, leading to nervous system diseases [20]. The above results show that the change of intestinal flora is closely related to the condition of IDD children, which can affect the immune system, nervous system and metabolic process of children. The imbalance of intestinal flora can be regarded as the disorder of spleen and intestine transformation, which is the embodiment of the imbalance of heart and brain.

#### **4.5 Immune system and IDD**

When the intestinal barrier is destroyed, it can stimulate the immune response and promote the secretion of immune active substances (such as interleukin-1, interleukin-6, etc.), which can penetrate the intestinal mucosa, enter the blood circulation, cross the blood-brain barrier, participate in neurodegeneration, repair, cause anxiety, depression, etc [21]. It has been suggested that the elevated

levels of these cytokines are closely related to various neuropsychiatric diseases, including depression, anxiety, autism and mental retardation [22]. The number of lymphocytes in some children with IDD is reduced, and the immune system is abnormal, which makes them vulnerable to virus infection or central nervous system damage through autoimmunity.

Short chain fatty acids (SCFAs) are the main metabolites produced in colon and play a key role in neuroimmunoendocrine regulation. Another mechanism of SCFA regulating systemic function is to promote the acetylation of lysine residues in nucleosome histones by inhibiting histone deacetylase (HDAC) activity. This intracellular signal transduction mechanism has been found in the gut and related immune tissues, as well as in the peripheral and central nervous systems. The formation of learning and long-term memory can be improved by enhanced histone acetylation, which can be improved by HDAC inhibitors. In addition to crossing the blood-brain barrier, SCFA seems to play an important role in maintaining its integrity, which is closely related to the controlled channels of molecules and nutrients from circulation to the brain, and plays a central role in brain development and the maintenance of central nervous system homeostasis. More and more evidences support the potential key role of SCFA in the signal transduction of brain gut axis, and this change of signal transduction may be the basis of central nervous system diseases, including neurodevelopmental disorders and neurodegenerative diseases [23].

## 5. Summary and Prospect

Nowadays, more and more attention has been paid to children with mental retardation by medical experts and all walks of life. More effective methods need to be explored in the treatment. The theory of brain gut axis is a hot topic in recent years. The important substances such as brain gut peptide, intestinal flora, immune system and central nervous system interact with each other through various mechanisms, and their changes will affect the interaction between gastrointestinal tract and brain, which can occur in early or postnatal period [20]. Although the term "brain gut axis" has not been recorded in traditional medicine, it can be concluded that there are similar theories from many aspects. Traditional Chinese medicine believes that the five zang organs and six Fu organs restrict each other, and that the theories of viscera dialectics, Qi blood body fluid dialectics, and mutualism have played an important role in the treatment of children with IDD, which are widely used in clinic. This paper discusses the relationship between the theory of heart spleen brain gut connection, brain gut axis and its influencing factors and the onset of IDD in children, which provides a new idea for the clinical treatment of mental retardation. However, more mechanisms between brain gut axis theory and children's IDD need further study.

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## References

- [1] Tang Jiulai, Fang Lingling, Wang Yizhen, Ma Bingxiang. *Progress in early intervention of mental retardation [J]. Chinese Rehabilitation Theory and practice*, 2020, 26 (08): 881-884.
- [2] Hong Xiaowen, Chen Yanhui. *Clinical and genetic analysis of 66 children with unexplained mental retardation [J]. Journal of Fujian Medical University*, 2019, 53 (03): 191-195.
- [3] Li Yan, Xiang Liling, Guo Hui, et al. *The effect of intestinal flora on central nervous system based on "the exterior interior of heart and small intestine" and the intervention of traditional Chinese medicine [J]. Chinese herbal medicine*, 2019, 50 (6): 1493-1498.
- [4] Lu dianqiang, sun Zhiguang. *Clinical application of "heart spleen correlation" based on brain gut axis [J]. Hebei Traditional Chinese medicine*, 2019, 08: 1257-1260.
- [5] Zhuang Jing, Wang Ruiping. *The correlation between the theory of heart and spleen and the theory of brain gut axis [j]. Chinese Journal of TCM information*, 2019, 09: 12-14
- [6] Wang HX, Wang YP. *Gut Microbiota-brain Axis. Chin Med J (Engl)*. 2016 Oct 5; 129(19): 2373-80. doi: 10.4103/0366-6999.190667. PMID: 27647198; PMCID: PMC5040025.
- [7] Lv Lina, Lin Kexin, Shao Jie. *Relationship between intestinal microflora and feeding and its communication with brain [J]. Chinese Journal of child health*, 2020, 10: 1114-1117.

- [8] Gao Kan, Mu Chunlong, Zhu Weiyun. *Research progress of microbe gut brain axis [J]. Acta microbiologica Sinica*, 2019, 09: 1737-1746.
- [9] González-Arancibia C, Urrutia-Piñones J, Illanes-González J, Martínez-Pinto J, Sotomayor-Zárate R, Julio-Pieper M, Bravo JA. *Do your gut microbes affect your brain dopamine? Psychopharmacology (Berl)*. 2019 May; 236(5): 1611-1622. doi: 10.1007/s00213-019-05265-5. Epub 2019 May 17. PMID: 31098656.
- [10] Sun Shuangxi, Bai Xiaoxin. *Understanding of brain gut axis from the perspective of TCM Physiology and pathology [J]. Shaanxi traditional Chinese medicine*, 2017, 06: 787-788.
- [11] Bai Yu, Hu Yunxia, Chen Junwei, et al. *Establishment of the theoretical system of bacteria brain gut axis [J]. Journal of Southeast University (Medical Edition)*, 2016, 35 (5): 781-785.
- [12] Vitamin A [J]. *Front Microbiol*, 2019, 10: 268. SHARON G, SAMPSON T, GESCHWIND D, et al. *The Central Nervous System and the Gut Microbiome [J]. Cell*, 2016, 167(4): 915-932.
- [13] Dinan, Timothy G, and John F Cryan. "Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration." *The Journal of physiology* vol. 595, 2 (2017): 489-503. doi:10.1113/JP273106.
- [14] Xinxin, Ren Lu. *Effect of intestinal flora on brain gut axis function through mast cells [a]. Psychosomatic medicine professional committee of Chinese society of integrated traditional Chinese and Western medicine. The 6th General Meeting of Psychosomatic Medicine Professional Committee of Chinese society of integrated traditional Chinese and Western medicine and the 12th Symposium on psychosomatic medicine of integrated traditional Chinese and Western Medicine [C]. Psychosomatic medicine professional committee of Chinese society of integrated traditional Chinese and Western medicine: Integrated Traditional Chinese and Western medicine Yes*, 2019: 9
- [15] Bates M. *Gut Feeling: Researchers Are Discovering a Link Between Depression and Gut Bacteria [J]. IEEE Pulse*, 2017, 8(6): 15-18.
- [16] FORSSBERG H. *Microbiome programming of brain development: implications for neurodevelopmental disorders [J]. Dev Med Child Neurol*, 2019, 61(7): 744-749.
- [17] Fröhlich EE, Farzi A, Mayerhofer R, Reichmann F, Jačan A, Wagner B, Zinser E, Bordag N, Magnes C, Fröhlich E, Kashofer K, Gorkiewicz G, Holzer P. *Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. Brain, Behavior, and Immunity*, 2016, 56: 140–155.
- [18] Zhou Feng, Zhou Zhiqiang, Ji Qing. *The role of intestinal flora in neuropsychiatric diseases [J]. Medical review*, 2019, 25 (23): 4690-4695
- [19] Tran SM, Mohajeri MH. *The Role of Gut Bacterial Metabolites in Brain Development, Aging and Disease. Nutrients*. 2021 Feb 25; 13(3): 732. doi: 10.3390/nu13030732. PMID: 33669008.
- [20] Jintong, Lin Fuqing. *The interaction between intestinal microorganisms and central nervous system [j]. Medical review*, September 2018: 1687-1692.
- [21] Liu S, Mi WL, Li Q, et al. *Spinal IL-33/ST2 signaling contributes to neuropathic pain via neuronal CaMKII-CREB and astroglial JAK2-STAT3 Cascades in mice [J]. Anesthesiology*, 2015, 123(5): 1154-69.
- [22] Petra AI, Panagiotidou S, Hatzigelaki E, et al. *Gut-microbiota-brain axis and its effect on neuropsychiatric disorders with suspected immune dysregulation [J]. Clin Ther*, 2015, 37(5): 984-995.
- [23] Silva YP, Bernardi A, Frozza RL. *The Role of Short-Chain Fatty Acids from Gut Microbiota in Gut-Brain Communication. Front Endocrinol (Lausanne)*. 2020 Jan 31; 11: 25. doi:10.3389/fendo.2020.00025. PMID: 32082260; PMCID: PMC7005631.