

# *Research Progress of Treating Infantile Anorexia from Liver and Spleen Based on Brain Gut Axis Theory*

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**Abstract:** infantile anorexia is a common functional disease with anorexia as the main symptoms. The function of liver and spleen in traditional Chinese medicine is similar to that of brain gut axis in western medicine. Brain gut axis acts directly or indirectly on the central nervous system through microorganisms, brain gut peptides and other substances, regulates intestinal effector cells, and then regulates appetite. Traditional Chinese medicine discusses infantile anorexia from the liver and spleen. Studies on its related prescriptions have found that traditional Chinese medicine acts on the brain gut axis by affecting intestinal microorganisms, promoting the secretion of motilin and digestive enzymes, and then plays a therapeutic role. It has the same effect as the brain gut axis of Western medicine in the treatment of infantile anorexia. Although the brain gut axis theory does not belong to the category of traditional Chinese medicine, it can further prove the scientificity of traditional Chinese medicine in treating infantile anorexia from the theory of liver and spleen, and provide theoretical basis and relevant clinical experience for the treatment of infantile anorexia with the combination of Chinese and Western medicine.

## **1. Introduction**

Infantile anorexia is a kind of functional disease, which is often seen in children's loss of appetite or no appetite. Children's long-term anorexia can cause their attention easily distracted, malnutrition, body weakness, growth retardation and other diseases. The location of anorexia in children is mainly in the stomach, closely related to the liver and spleen. A spleen deficiency for a long time, spleen loss of health transport, leading to aggravation of anorexia. Second, the family, society, schools and other environmental reasons lead to poor children's emotions, liver depression by the soil, soil loss of health transport, children anorexia will arise from this. With the further study of brain gut axis theory, brain function and intestinal function can interact. The central nervous system of the brain regulates gastrointestinal function by means of immunity and neuroendocrine. At the same time, abnormal gastrointestinal function can react on the brain and cause emotional distress in children. Children with anorexia in addition to digestive symptoms, often accompanied by emotional changes, such as irritability, restless, indifferent expression. Some studies have shown that the onset of anorexia in children is closely related to appetite regulation and microbial metabolites in the brain-gut axis. The specific mechanism of treating infantile anorexia from the perspective of liver and spleen in traditional Chinese medicine is not clear, but the function of liver

and spleen in Traditional Chinese Medicine(TCM) is similar to that of brain - intestine axis. Therefore, we can explore the mechanism of TCM treatment of infantile anorexia from liver and spleen through brain-gut axis theory, and provide theoretical basis and clinical experience guidance for traditional Chinese and Western treatment.

## 2. Relationship between Brain-Gut Axis and Liver and Spleen Function

Brain-gut axis is mainly composed of brain, intestine, microorganism and so on. It can realize bidirectional regulation of central nervous system and gastrointestinal function by regulating microorganism and brain-gut peptide. The liver controls dispersal, and it has the function of regulating emotion, which corresponds to the brain regulating emotion in western medicine. The spleen governs transportation and transformation and corresponds to the digestion and absorption of the intestine in western medicine. Therefore, to explore the relationship between “liver and spleen” of TCM and brain intestinal axis of modern medicine is of great significance to the study of infantile anorexia.

### 2.1 Physiological Correlation

In the meridians, the liver and spleen are connected with the brain through the meridians. “*Lingshu · Meridian*” said: “The Foot Jue Yin Liver Meridian... To the lower abdomen... Up into the larynx, connected to the eye system, up out of the forehead, and the head of the du. Foot taiyin spleen meridian... Into the abdomen... Connect the tongue, scatter under the tongue.” It shows that the liver and spleen are connected with the brain on the meridians. However, both the liver and spleen pass through the large intestine and the small intestine, indicating that the liver and spleen are on the meridians or related to the brain and intestine. In terms of viscera function, the liver controls emotion, and the prefrontal lobe of the brain controls people's mental emotion. Therefore, the physiological function of the liver is similar to that of the brain. The spleen is the main transporter of water and grain into fine matter, and transport the fine matter to the organs and organs of the human body, so as to nourish the organs and provide the source power for their normal operation. The small intestine is the first place for digestion and absorption of the human body, while the large intestine reabsorbs the food residue conducted by the small intestine. Therefore, the function of the spleen in TCM is similar to that of the intestine in western medicine

### 2.2 Pathological Interaction

In terms of meridians, brain, intestine, liver and spleen are closely related. In view of encephalopathy and enteropathy can be treated by acupuncture of liver meridian and spleen meridian, Such as: acupuncture spleen Sanyinjiao, liver Taichong treatment due to encephalopathy (cerebral hemorrhage, cerebral infarction, cerebral embolism, brain trauma, etc.) caused by physical activity disorders; Abdominal pain (enteritis in western medicine) was treated by acupuncture at spleen point Taibai and liver point Taichong. At the same time liver and spleen diseases can be treated by scalp acupuncture, abdominal acupuncture, such as abdominal acupuncture can treat abdominal pain, diarrhea and other spleen diseases and headache, dizziness and other liver diseases. Abdominal acupuncture can also treat liver diseases such as distension and vertigo, and spleen diseases like stomachache and abdominal pain. In terms of viscera, If the liver loses its function, the Qi regulating mechanism is out of balance, and the spleen will not rise and clear, the subtle substances will not nourish the brain and marrow, and the symptoms of brain apathy and emotional disorders will easily appear, such as memory loss, depression, dull expression. Spleen failure, prone to gastric distention, abdominal distention phenomenon, resulting in slow intestinal peristalsis,

digestion and absorption capacity weakened. Enteropathy (mechanical ileus, Crohn's disease, etc.) often accompanied by abdominal distension, abdominal pain and other symptoms of splenic diseases. Encephalopathy can lead to emotional abnormalities, functional dyspepsia and other liver and spleen diseases. In addition, the liver likes catharsis and reaches, and hates depression. Liver dysfunction is manifested as emotional depression, mental depression, depression, indifferent expression and other emotional abnormalities. And then affect the spleen (intestinal absorption) transport function. If the spleen is dysfunctional and the essence of Qi and blood is insufficient, the liver will lose nourishment, the liver Yin is insufficient, Yin does not converge Yang, and the liver Yang is violent, there will be manifestations of emotional failure. The emotional failure caused by liver loss and catharsis is similar to the abnormal emotional performance of the brain. It indicates that there is bidirectional regulation between liver and spleen and affects the function of brain and intestine.

### 3. Brain-Gut Axis is Involved in the Pathogenesis of Anorexia in Children

Brain-gut axis plays a role in infantile anorexia mainly through regulating neuroendocrine. Brain and intestine can secrete a variety of peptide hormone substances, which affect gastrointestinal motility peptide hormone more than 10 kinds. The common brain gut peptide hormones that stimulate gastrointestinal motility include motilin, gastrin, somatotropin, substance P, 5-hydroxytryptamine, etc. Brain-gut peptides that inhibit gastrointestinal motility include cholecystokinin, vasoactive peptide, somatostatin, calcitonin gene-related peptide, neurotensin, neuropeptide Y, leptin, nitric oxide, etc. Through these neurotransmitters, peptide hormones act on the hypothalamus, medulla oblongata, spinal cord and gastrointestinal system, and then regulate gastrointestinal function and mood. Infantile anorexia is associated with appetite. The centers that control appetite are located in the arcuate nucleus of the hypothalamus (ARC) and the paraventricular nucleus of hypothalamus (PVN). The nervous and circulatory system regulates appetite by acting on the hypothalamic arcuate nucleus. The function of the hypothalamic arcuate nucleus is divided into two parts: the first part suppresses appetite by expressing cocaine-amphetamine-regulated transneurons and neurons (CART) regulated by preopiomelanin-corticosteroid (POMC), The other part promotes appetite by expressing neuropeptide Y and agouti associated protein, which control appetite through PVN of hypothalamus. Different brain-gut peptides have different functions. There are two models of long-term and short-term appetite regulation. Long-term appetite regulation is mainly related to fat storage, when fat accumulation is excessive, leptin secreted increased, leptin passed the visceral afferent nerve and acted on ARC, and inhibited appetite by regulating CART and POMC. The short-term regulation of appetite is through cholecystokinin, YY peptide, gastrin and other substances secreted by intestinal endocrine cells, acting on ARC via G protein-coupled receptors to inhibit neuropeptide Y and agouti associated protein increase satiety<sup>[1]</sup>.

Studies have shown that microbes play an important role in the development of the brain-gut axis and anorexia in children .The content of Lactobacillus and Bifidobacterium in the intestines of children with anorexia was lower than that of normal children, and the number of Enterobacteriaceae increased. It was also related to the decrease of Bacteroides and the increase of the levels of actinomycetes and verrucous bacilli<sup>[2]</sup>. Studies have shown that infantile anorexia is closely related not only to the type and quantity of intestinal microorganisms, but also to the maturity of microorganisms. In addition, intestinal bacterial components and metabolites can also affect intestinal satiety, and then regulate the host's satiety and appetite<sup>[3]</sup>. Metabolic products of the gut microbiota regulate appetite through the following aspects: 1. Peripheral circulation regulation, serotonin is an important neurotransmitter in the brain-gut axis, and intestinal microbiome may

influence appetite through 5-hydroxytryptamine. SCFA stimulates serotonin production and release in the colon, which in turn activates the release of anorexic hormones GLP-1 and PYY into the peripheral circulation. This pathway is regulated by the hypothalamus, ultimately influencing eating behavior and appetite<sup>[1]</sup>. Immunomodulatory, the intestinal microbiota produces small protein sequences and microbiologically derived toxins. The gut microbiota produces a protein sequence similar to the human body's regulation of appetite and promotes the production of immunoglobulins, which effectively reduces the degradation rate of gut-derived hormones and the neuroendocrine factor ghrelin, and may trigger an autoimmune response. For example, *E. coli*, one of the most important microbiota in the gut, produces the hydrolytic protease B (ClpB), which is elevated in anorexia nervosa associated with inadequate food intake. ClpB and intestinal microbiologically derived toxins are highly affected by gut barrier integrity. Intestinal microbiologically derived toxins can induce immune response, which may lead to decreased taste receptor cell differentiation and taste detection. These taste receptor cells also express the anorexic hormones GLP-1, PYY, and cholecystokinin, a pathway regulated by the hypothalamus that ultimately affects eating behavior and food-related behavior<sup>[4]</sup>. Neuromodulation, metabolic products of intestinal microorganisms (SCFA, bile acids, neuroactive substances, etc.) can act on intestinal receptors, It can promote the production of intestinal L cells or vagus nerve, promote the release of anorexic hormone PYY and GLP-1 from gastrointestinal L cell. These effects are mediated by G protein-coupled receptors (GPCR), FFA receptor 2 (FFA2 / GPR43) and FFAN receptor 3 (Ffa3 / Gpr41), which stimulate the sympathetic and autonomic nerves to regulate appetite<sup>[5]</sup>. The metabolic products of intestinal flora act on the central nervous system through the peripheral circulation, immune and nervous system pathway, further affect the host food intake, and form the microbial-brain-gut axis system. In conclusion, infantile anorexia is closely related to microbial-brain-gut axis.

#### 4. Research Progress of Tcm in the Treatment of Pediatric Anorexia from Liver and Spleen

The physiological characteristics of children are: “The liver is often surplus, the spleen is often insufficient”, the physiological characteristics of the children's five internal organs are not filled, the five aspirations are still existing, the seven emotions are gradually prepared, the occasional emotional stimulation, the seven emotions are injured, it will start from the liver, the liver has more than enough, it will hurt the spleen, indicating that pediatric diseases are mostly related to the liver and spleen. “*Complete works of Chishui Xuanzhu· Volume 13*” “Those who cannot eat, by the spleen and stomach are weak, or after the illness and the spleen and stomach qi has not recovered, or the phlegm is scorched, so they do not think about eating”. It shows that anorexia is closely related to the spleen and stomach, and spleen and stomach weakness or spleen and stomach loss can cause anorexia. “*Pediatric Drug Certificate Direct Decision*” “Spleen and stomach disharmony, can not eat milk”, further explains that poor spleen and stomach function and pediatric anorexia are closely related. Pediatric anorexia is located in the stomach and is closely related to the liver and spleen. The main gastric acceptance is cloudy, the spleen is mainly transported to clear, the spleen and stomach are the hub of the lifting and lowering of the gas machine, the main drainage of the liver can regulate the lifting and lowering of the human body's qi machine, the spleen transport depends on the normal drainage of the liver, the liver qi is smooth, the spleen is transported smoothly, the stomach is lowered, and the stomach can be absorbed, indicating that pediatric anorexia should be treated from the liver and spleen. Pediatric anorexia is mainly divided into five major types: damp heat of spleen and stomach, loss of healthy movement of spleen and stomach, Qi deficiency of spleen and stomach, yin deficiency of spleen and stomach, spleen deficiency and liver hyperactivity. The spleen and stomach damp and hot type treatment is to clear the heat and awaken the spleen, and Suping Yu uses Xiehuang powder to treat damp heat of spleen and stomach with an effect of 86%<sup>[6]</sup>.

Loss of healthy movement of spleen and stomach type is based on healthy spleen digestion, the effective rate of Jianpi Xiaoshi Kaiwei recipe in the treatment of infantile anorexia was 97.5%, which was significantly higher than that in the control group<sup>[7]</sup>. Jinhua Xu draw up a Jianpi Yiqi recipe has an effective rate of up to 96.23% in the treatment of infantile anorexia with spleen and stomach deficiency<sup>[8]</sup>. The effective rate of Yangyin Yunpi recipe prepared in the treatment of infantile anorexia with yin deficiency of spleen and stomach was significantly higher than that in the control group of Western medicine<sup>[9]</sup>. Xu Jianping used yinshao Liujunzi recipe to treat infantile anorexia of liver hyperactivity and spleen deficiency. The total effective rate was 98%<sup>[10]</sup>. Numerous clinical observations have shown that the hepatosplenic theory of TCM has a significant effect on the treatment of pediatric anorexia.

## **5. Tcm from the Liver and Spleen to Treat Pediatric Anorexia Prescription Drugs and the Relevant Mechanism of Regulating the Brain-Intestine Axis.**

Professor Huifu Xu More than 70% of the Chinese medicines used in the prescription medicines for the treatment of anorexia in children from the liver and spleen are: large-headed atractylodes, Hawthorn, Chicken's gizzard-membrane, Poria, Malt, licorice, Millet sprout, Magnolia bark. The main components of large-headed atractylodes are polysaccharides, endolipids, and volatile oils, and studies have shown that large-headed atractylodes can effectively regulate gastrointestinal hormones such as gastrin, growth hormone, and vasoactive intestinal peptides in rats, and significantly improve their gastrointestinal function. In addition, large-headed atractylodes polysaccharides help gastrointestinal, bacillus, and lactobacillus to grow in vitro, and the growth of the bacteria is positively correlated with the concentration of leuko polysaccharides<sup>[12]</sup>. Hawthorn is rich in vitamin B2, vitamin C, organic acids, carotene, which can promote the secretion of digestive enzymes and increase the activity of gastric enzymes. Among them, organic acids can promote intestinal peristalsis, reduce the expression of 5-HT and 5-HT3R in rats with irritable bowel syndrome, and weaken gastrointestinal motility and secretion, so hawthorn water extract has a two-way regulatory effect on gastrointestinal smooth muscle<sup>[13]</sup>. Chicken's gizzard-membrane can regulate the movement of the small intestine in both directions, improve the gastric emptying rate and small intestine propulsion rate of rats with indigestion caused by dilute hydrochloric acid, increase the content of gastrin and motilin in the serum, and improve gastrointestinal function<sup>[14]</sup>. Poria is mainly based on triterpenoids and polysaccharides, and poria water extract can inhibit urease, thereby inhibiting HP production and promoting gastric mucosal hyperplasia. Poria water extract can effectively inhibit intestinal bacteria and Staphylococcus aureus and other pathogenic bacteria, thereby improving the intestinal flora<sup>[15]</sup>. Malt contains  $\alpha$ -,  $\beta$ -amylase, proteolytic enzyme, isomaltooligosaccharide fructose, which can improve the intestinal flora in both directions. Glycyrrhiza chalcone A in licorice can protect gastric mucosa, inhibit the release of inflammatory factors, promote gastric juice secretion and increase pepsin activity. Malt sprouts contain amylase which can promote the digestion of starch. Magnolia bark contains ethyl acetate can enhance gastrointestinal motility, enhance blood gastrin secretion, promote intestinal peristalsis emptying, by changing intestinal flora, produce motilin, promote the secretion of digestive enzymes to improve intestinal motility<sup>[16]</sup>. TCM is rich in chemical components, in addition to a single drug itself has a variety of ketones, polysaccharides, alkaloids and other chemicals in the body to produce effects, In the process of decocting herbs, the physical and chemical reactions produced by the interaction of many kinds of Chinese herbs make the pharmacodynamic effect offset or enhanced, or produce new effective substances. Therefore, to study the pharmacological response of TCM, we should not only study single Chinese herbs, but also study the pharmacology of compound Chinese drugs in treating diseases. Child appetizer mixture promoting digestive enzyme secretion and affecting appetite

regulating factors. The contents of Scamp3 and Tmem86a decreased in children with anorexia after treatment with Child appetizer mixture. The content of Smarcc1, Nudt13, Rpp30 and Glmp increased<sup>[17]</sup>, which indicated that the mechanism of multi-component and multi-target was presented in the treatment of infantile anorexia. Therefore, the target of treating infantile anorexia from liver and spleen is brain - intestine axis.

## 6. Conclusion

It is found that TCM mainly treats infantile anorexia from liver and spleen, its treatment method is to clearing heat and invigorating the spleen, invigorating the spleen and digestion, supplementing qi and spleen, benefiting Yin and transporting the spleen, calming the liver and strengthening the spleen. TCM can improve the balance of intestinal microflora, promote the secretion of motilin and digestive enzymes, and then affect the brain-gut axis on gastrointestinal cells. Western medicine uses probiotics to influence the metabolites of gut bacteria, which regulate appetite through the brain-gut axis to treat anorexia in children. TCM and western medicine in the treatment of infantile anorexia, although the theory is different, but its treatment in children anorexic has the same effect, and the same disease with different treatment of TCM. Liver and spleen are highly correlated with brain-gut axis in physiology, and interact with each other in pathology. TCM treatment of infantile anorexia target more, can be through microbiology, molecular biology, multiomics and other modern medical science and technology, explore the specific target of Chinese herbal medicine treatment infantilism, These targets and western medicine treatment of children anorexia whether there is common, for the development of these targets for Chinese medicine to provide theoretical support, but also for the combination of Chinese and Western medicine to treat child anorexia provide theoretical basis and clinical guidance.

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