

The Treatment of Functional Dyspepsia Based on "Brain-gut Co-regulation" Theory

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Abstract: Functional dyspepsia is a typical functional gastrointestinal disease with a high incidence and a long course of disease that is difficult to cure, its pathogenesis can be summarized as "imbalance of the central center of the gods" and "blockage of the stomach and intestines". Now we take the idea of "Brain-Gut Coordinating" as an overall guide, and specifically use methods such as invigorating spleen and soothing liver and regulating the mind, pungent open and bitter down bearing and regulating center. In order to improve the patient's digestive symptoms and relieve the patient's mental and psychological discomfort, so as to achieve better clinical efficacy, and providing new ideas for the treatment of functional dyspepsia.

Keywords: Brain-Gut Co-regulation, Brain-gut axis, Functional dyspepsia.

1. Overview of FD

Functional dyspepsia (FD) refers to a disease with long-term symptoms such as postprandial fullness and discomfort, early satiety, epigastric pain, and epigastric burning, and endoscopy does not show any organic lesions. The global prevalence of the disease is relatively high, accounting for about 7%–45% [1], and the pathogenesis is relatively complex, and it is currently believed that it is mainly related to gastrointestinal motor dysfunction, visceral hypersensitivity, abnormal cerebro-intestinal peptide levels, and psychological factors [2], and the latest Rome IV criteria define its core pathogenesis as abnormal brain-intestinal interaction [3]. The brain and intestines in the human body are connected by a complex neuro-endocrine-immune system to form a system, namely the brain-gut axis, which involves the central nervous system, the autonomic nervous system and the enteric nervous system, and there is a substance with the dual functions of hormone secretion and neurotransmitter conduction between the brain-gut axis - brain-gut peptide, which is widely distributed between the nervous system and the gastrointestinal tract, and has the function of regulating gastrointestinal motility, sensation, and hormone secretion, and there are more than 60 kinds of cerebro-intestinal peptides found at present [4]. Among them, motilin (MTL), gastrin (GAS), vasoactive intestinal peptide (VIP), cholecystokinin (CCK), Ghrelin and other cerebroenteric peptides are associated with FD. Due to the long course of FD disease and the difficulty of healing, which seriously affects the quality of life of patients, it is easy to cause people to have a series of anxiety, depression, nervousness and other emotions, and at the same time, anxiety, depression and other adverse emotions will also lead to a decrease in vagus nerve activity, thus causing a series of gastrointestinal symptoms.

In traditional Chinese medicine, FD is classified as "gastric stuffiness" and "stomach pain" according to its main symptoms, and it is often caused by factors such as infection with external pathogens, unclean diet, emotional imbalance, and excessive fatigue. The spleen governs ascending, while the stomach governs descending. The spleen and stomach are the crucial hubs for the ascending and descending of the body's qi. When the ascending and descending of the spleen

and stomach are unobstructed, the flow of qi throughout the body is smooth. However, if there is a disturbance in the ascending and descending of the spleen and stomach, it can lead to obstruction of qi flow, resulting in illness. Therefore, the core pathogenesis of FD lies in the imbalance of the ascending and descending of qi, which is also the key pathological link to its recurrence [5]. Additionally, the ascending and descending of qi in the middle jiao relies on the liver's function of governing the free flow of qi. If the liver's qi stagnation counteracts the spleen's earth element, it can impact the smooth flow of qi in the middle jiao, leading to the development of this disease. The text from Li Gao's *Treatise on the Spleen and Stomach* said: "All anger, anger, sorrow, thought, fear, and fear all damage the original qi. The yin-fire is blazing, and the heart is stagnant, and the seven emotions are uneasy... When a person sees what he wants to do, he suddenly recovers from his illness, which is the reason why the original qi in his stomach is dredged." It not only expounds the influence of emotions on the mind and the body, but also mentions the importance of soothing emotions and harmonizing the spleen and stomach in the treatment of diseases.

2. The Theory of "Brain-gut Co-regulation"

Wei Wei et al., after inheriting the academic thought of Lu Zhizheng, a master of traditional Chinese medicine, of "holding middle jiao the spleen and stomach, nourish the surrounding viscera, relax the mood, regulate the rise and fall, take into account the dampness and dryness, and make the spleen and stomach normal storage and transportation", further put forward the theory of "regulating the pivot and opening the stomach", and under the guidance of this theory, according to the characteristics of functional gastrointestinal diseases, summarized the pathogenesis as "spirit pivot (brain) imbalance" and "gastrointestinal qi disorder (intestine)", so they proposed the treatment method of "brain-gut co-regulation" [6].

In *Lingshu-Meridian* it is said that "at the beginning of human life, essence is formed first, and after essence is formed, the brain and marrow are created". In traditional Chinese medicine, the "brain" is referred to as the residence of the

primordial spirit, commanding all spirits, and capable of leading the body's mental consciousness, sensory perception, thoughts, and emotions, similar to the function of the central nervous system in modern medicine. In addition, in *Plain Questions-the secret classics of Linglan*, it is stated that "the heart is the office of the sovereign, where the spirits and intelligence emerge"; and in *Lingshu-Xieke*, it is said that "the heart is the chief of the five Zang organs and six Fu organs, and the dwelling place of the spirit", showing that the heart is the root from which spirits and intelligence emerge, and the brain is where spirits and intelligence flow. It can be seen that the heart is the root of the spirit, the brain is the place where the spirit flow, the brain controls the original spirit, and the heart controls the subjective spirit awareness, that is, "the body of the spirit is hidden in the brain, and the use of the spirit is in the heart", and the heart and brain are jointly in charge of the spirit [7]. The liver governs emotions, while the liver stores the soul, which is one of the Five Spirits. Although the emotions are regulated by the liver, their function is in the brain. Therefore, the functions of the heart and liver are governed by the "spirits" located in the brain. In *Lingshu-Benshu*, it is mentioned: "The large intestine and small intestine both belong to the stomach, which is the Foot Yangming aspect." Therefore, in the concept of "Brain-gut Co-regulation", the "gut" refers to the entire digestive system including the spleen, stomach, and small and large intestines, with the main function of receiving, fermenting, digesting, and excreting food and fluids. In *Lingshu-Wulong Jingye Bie*, it is stated: "The essence of the five grains, when combined and transformed into nourishing essence, seeps into the bone cavities to nourish the brain and marrow." When food and drink enter the stomach, undergo fermentation and digestion in the gastrointestinal tract, some nutrients are transported upward to nourish the brain and marrow, providing a material basis for the brain to govern spirits and regulate the physiological functions of the internal organs. It can be seen that the brain and gut interact and influence each other, forming an organic whole. Therefore, the treatment method of "brain-gut co-regulation" is to take into account the mental and mental conditioning while differentiating and treating different symptoms to restore the gastrointestinal characteristics based on pattern identification, and not only regulate the digestive tract-related discomfort symptoms, but also regulate people's mental and emotional abnormalities [8].

From the perspective of traditional Chinese medicine, the brain and intestines are connected via the Foot Yangming Stomach meridian. From the perspective of modern medical research, there is also a bidirectional information pathway between the brain and the gastrointestinal tract known as the "brain-gut axis." The "brain" and "intestines" have close physiological and pathological interactions, and therefore, the use of the "brain-gut co-regulation" therapy aims to consider both the brain and intestines, with a multi-target, multi-dimensional approach to treatment. This holistic approach seeks to achieve better treatment outcomes for functional dyspepsia.

3. "Brain-gut Co-regulation" Theory for Treating FD

3.1 Strengthen the Spleen and Regulate qi and Mind-claiming Theory

The pathogenesis of FD lies in the weakness of spleen Qi and the stagnation of stomach Qi circulation within the middle jiao, leading to stagnation of stomach Qi and abnormal ascending and descending functions of the spleen and stomach. The theory of Spleen deficiency and qi stagnation as the root is closely related to various mechanisms of FD gastrointestinal motility disorders and visceral hypersensitivity [9]. In the *Huangdi's Internal Classic*, it is stated that "Central produce wet ... In viscera for the spleen... In the will for thinking. Excessive overthinking damages the spleen, and anger prevails over excessive thinking." If excessive worrying leads to stagnation of middle jiao Qi circulation and inefficient transformation and transportation of food in the spleen and stomach, it can result in epigastric pain due to stagnation, or prolonged thinking can harm the spleen, leading to abnormalities in spleen and stomach function and the manifestation of distention. In the treatment of FD patients with spleen deficiency with qi stagnation pattern, herbal formulas are often prescribed to regulate qi and strengthen the spleen. Jianpi Liqi Formula is commonly used in clinical practice, although different doctors add or subtract different medicines, with most of them utilizing herbs such as *Codonopsis Pilosula*, *Atractylodes Macrocephala*, and *Poria Cocos* as principal herbs, with *Agastache*, *Amomum*, and *Magnolia Officinalis* as assisting herbs. The main focus is on invigorating the spleen and regulating Qi, supplemented with the functions of calming the mind and promoting Qi flow, aiming to achieve therapeutic effects on symptoms and mental aspects.

Clinical studies [10] on Liqi Jianpi Formula have shown improvements in symptoms such as epigastric distension, poor appetite, belching, and loose stools in FD patients, along with reductions in Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) scores. Compared to Western medication, the use of these formulas has shown more significant improvements in symptoms and mental health, indicating their potential to enhance clinical efficacy, alleviate symptoms, regulate emotional disturbances, and improve mental disorders in FD patients. Research [11] suggests that Jianpi Liqi Formula can reduce the expression of corticotropin-releasing factor (CRF) and its receptor CRF-R1 in the duodenum of FD rats. CRF is an important mediator in the brain-gut axis related to gastrointestinal motility and visceral hypersensitivity, and these formulas may modulate CRF-related pathways to achieve symptom improvement. Furthermore, under stress conditions, increased intestinal substance P content can activate eosinophils to release corticotropin-releasing hormone (CRH), which further activates mast cells to release various inflammatory factors, leading to duodenal micro-inflammation. Jianpi Liqi Formula can inhibit this pathway, down-regulate the expression of related inflammatory signaling molecules, and improve duodenal micro-inflammation.

3.2 Soothe the Liver and Harmonize the Stomach and Relieve Depression

Among the five viscera, the liver governs dispersion and regulation, promoting the smooth flow of qi, and the influence of the seven emotions and internal injuries on the viscera qi is the most common, and the foot syncope yin and liver meridians "go up into the jaws, connect the eyes, go up and

out of the forehead, and meet with the pulse at the top", which is connected with the brain meridians, which shows that the heart, brain, and god center are closely related to the liver. There are statements in *Theory of Blood Syndrome*: "The nature of wood is mainly to drain, and the food qi enters the stomach, thanks to the qi of the liver and wood to relieve it." If the liver qi is stagnant, the liver and gallbladder are incompetent, and the wood is not thinned, it will cause the spleen and stomach to be blocked, the distribution will be weak, and the abdomen will be full, full, belching and other manifestations will appear, and the symptoms and emotions will affect each other, which will worsen over time and be difficult to treat. Starting from the theory of brain-gut co-regulation, on the basis of the treatment of FD spleen and stomach, it is provided with products that relieve liver and regulate qi, relieve depression and calm the nerves, and pay attention to the conditioning of the mind and mind when treating the liver and spleen, in order to achieve better treatment results.

Studies [12] have confirmed that after the treatment of liver soothing and spleen strengthening method, the gastric emptying and small intestine propulsion function of FD rats with liver depression and spleen deficiency were enhanced, the expression of MTL and GAS in the antral tissue increased, and the expression of VIP decreased, that is, the effect was achieved by improving gastrointestinal motility and promoting gastric emptying. Relevant studies [13] have shown that FD rats with liver depression and spleen deficiency can promote gastric motility by down-regulating the CNP/NPR-B/cGMP signaling pathway after the intervention of Pingwei Capsule, and the improvement of mental state of rats is better than that of ordinary gastric motility drugs. Chaihu Shugan San is mainly used to treat the stagnation of liver qi caused by unsatisfactory emotions and liver wood loss of free will, and the meridian qi is unfavorable, so the mainly takes Bupleurum as the Monarch medicines to relieve the liver and relieve depression, and Rhizoma Cyperi and Chuanxiong Rhizome are the Minister medicines to regulate qi and relieve pain and help Bupleurum to relieve the liver, and there are also Tangerine Peel, Fructus Aurantii, Radix Paeoniae Alba, Radix Glycyrrhizae and other medicines to play the role of soothing the liver and promoting qi, invigorating blood and relieving pain. Clinical studies [14] have found that FD patients not only have a great improvement in gastric emptying rate, but also have a decrease in anxiety self-rating scale and depression self-rating scale scores after treatment with Chaihu Shugan San, which shows that Chaihu Shugan San can play a therapeutic role in gastrointestinal symptoms and anxiety and depression in FD patients.

3.3 Pungent Dispersing and Bitter Descending and Regulating the Pivot Method

FD takes spleen deficiency and qi stagnation as the basic pathogenesis, and the spleen deficiency is unfavorable in the rise and fall of the coke machine, and the upper heat cannot be released, and the lower cold cannot be served, so it is easy to develop as a syndrome of mixed cold and heat, and the clinical manifestations are mostly dry mouth, bitter mouth, loose stool, and pale yellow tongue. Banxia Xingxin soup comes from "Treatise on Febrile Caused by Cold" "However, if the

symptoms are full but not painful, it is called stomach ruffian...It is advisable to take Banxia Xiexin Decoction", this recipe takes Banxia as the Monarch medicine, Banxia dry ginger is matched with pungent dispersing to disperse masses, skullcap and coptis are bitter descending to remove the full, and then add ginseng, licorice, and jujube to adjust the deficiency of middle jiao, and reconcile the disadvantage of the cardinal in the middle of the spleen and stomach, and restore the function of the spleen and stomach to rise and fall with the method of pungent dispersing and bitter descending.

Previous studies [15] have shown that the FD model rats who have undergone the intervention of Banxia Xingxin decoction tend to have normal gastric emptying and small intestine propulsion, and the gastrointestinal sensitivity is significantly reduced, and can act on the "brain-gut axis" by regulating the adrenocorticotropin-releasing factor (CRF) pathway and related brain-gut peptide content, thereby improving the symptoms related to FD. Relevant clinical studies [16] have found that the pungent dispersing and bitter descending method can change the gastrointestinal hypersensitivity state by reducing the fasting and postprandial serum serotonin (5-HT) levels in FD patients, and can also regulate the proximal gastric capacity by reducing the serum nitric oxide (NO) level in patients, that is, by regulating visceral hypersensitivity and gastric capacity abnormalities to treat the disease. The results [17] showed a decrease in Hamilton Anxiety Scale scores, Hamilton Depression Scale scores among treated FD patients, and significant improvement in the scores of two dimensions of physiological function and mental health in the SF-36 scale evaluation of quality of life, indicating that the method of acidity to disperse and bitterness to descend effectively improves symptoms such as abdominal distension, early satiety, upper abdominal pain, belching in FD patients, and also has a significant effect on improving patient anxiety and depression.

3.4 Acupuncture for Harmonizing the Viscera, Brain, and Intestines

Acupuncture therapy, as a major feature of traditional Chinese medicine treatment, is increasingly being recognized for its effects on various neurological systems in the human body. Some scholars believe that functional gastrointestinal disorders can be treated using the method of regulating the spirit and selecting acupuncture points. By focusing on both "regulating the spirit" and "harmonizing emotions," this approach aims to facilitate the coordination of the body's functions and promote the circulation of Qi and blood, as well as improve emotional disorders such as anxiety and depression. This comprehensive regulation of the body helps eliminate gastrointestinal discomfort symptoms at their root and enhances treatment efficacy [18]. In the treatment of functional gastrointestinal disorders FD, some practitioners emphasize the interplay between the organs, emotions, and Qi circulation. They suggest treating the heart and stomach together and harmonizing the brain and intestines [19]. Acupuncture points such as Shenmen, Benshen, and Shenting are selected to calm the mind, while points like Sanyinjiao, Zusanli, Hegu, and Taichong are chosen to regulate the liver and intestines. By employing the "spirit-regulating needling technique" to simultaneously address the physical and mental aspects, emotional balance can be restored to treat FD

effectively.

Studies have found that acupuncture at Hegu and Taichong points can impact the redistribution of blood flow in the brain, activate specific brain regions, and regulate digestive system function while also combating anxiety, depression, and insomnia [20]. One of the primary mechanisms of acupuncture therapy for FD involves restoring various neurological functions and regulating brain-gut peptides to reestablish the overall communication pathway of the brain-gut axis. This therapy can alleviate anxiety and depression in FD patients by modulating the brain-gut interaction pathways, influencing brain function or neural reflexes, and improving digestive symptoms such as abdominal pain and bloating. Additionally, it can regulate the expression of brain-gut peptides and adjust intestinal microbiota content to effectively treat FD [21]. Based on the theory of brain-gut co-regulation, research teams have conducted clinical studies [22] on FD patients treated with acupuncture. Patients receiving acupuncture at Baihui, Shenting, Yintang, Zhongwan, and Zusanli points showed significant improvement in clinical symptoms. Moreover, compared to a control group treated solely with prokinetic drugs, the acupuncture group exhibited notable reductions in HAMA and HAMD scores, as well as improvements in the Nepean Dyspepsia Index scores, indicating the significant effectiveness of harmonizing the brain and intestines through acupuncture therapy. In conclusion, acupuncture treatment has significant effects on regulating both the "brain" and "Gastrointestinal".

4. Conclusion

Nowadays, people's lives are becoming more and more stressful, and more attention is paid to the health of the body, and various psychosomatic diseases are becoming more and more common. As a typical digestive psychosomatic disease, the influence of FD psychological factors on the disease deserves the attention of every clinician. Aiming at the core pathogenesis of FD, which is the core pathogenesis of FD, the treatment method of "brain-gut co-regulation" is adopted, giving full play to the advantages of the overall concept of TCM and syndrome differentiation and treatment, and carrying out two-way multi-target regulation therapy from the brain and intestine, so as to shorten the course of the disease and improve the efficacy. The diagnosis and treatment idea of "brain-gut co-regulation" is supported by traditional Chinese medicine theory and modern medical scientific data, which provides a new idea for the clinical treatment of FD and a certain reference for the diagnosis and treatment of other digestive psychosomatic diseases.

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