

Research Progress on the Mechanism of Action of Acupuncture in the Treatment of Chronic Functional Constipation

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Abstract: *With the acceleration of the pace of life, the increase of social pressure and the change of dietary structure, chronic functional constipation (FC) has gradually become a common disease that plagues people's normal life, among which slow transit constipation (STC) is the most common. Chronic constipation not only induces a series of anorectal diseases, but also leads to insomnia, anxiety and other psychological problems, which increases the risk of cardiovascular and cerebrovascular diseases for the elderly. Although Western medicine treatment can improve symptoms, the prognosis is often poor, while traditional acupuncture is a green treatment that is simple and easy to implement, with definite efficacy and obvious advantages. This article reviews the research progress on the mechanism of acupuncture in the treatment of chronic functional constipation, aiming to provide enlightenment for clinical treatment.*

Keywords: Constipation, Functional constipation, Pathogenesis, Acupuncture.

1. Introduction

Constipation is a common digestive disease, it is the state of defecation process is not smooth, accompanied by defecation difficulties and fecal dryness and other symptoms, and the number of bowel movements is less than 2 to 3 times a week. Differences in the causes of constipation lead to differences in the types of constipation, which can be divided into two types: organic constipation and functional constipation [1]. The prevalence of chronic functional constipation ranges from 4 to 6 per cent among adults in China, up to 22 per cent in people over 60 years of age, and up to 25 per cent in Western countries [2]. Chronic constipation can lead to a higher incidence of anorectal diseases such as anal fissures, haemorrhoids and rectal prolapse [3]. Increased risk of cardiovascular disease in older people [4]. Patients with severe constipation often suffer from insomnia, anxiety, depression and irritability, which affect their physical and mental health and quality of life [5]. For the treatment of chronic functional constipation, long-term use of Western medicine can lead to intestinal flora imbalance and weaken intestinal motility, and acupuncture traditional treatment has the advantages of simplicity and ease of use, outstanding efficacy, no side effects, etc., and it has a broad prospect of clinical use [6]. By reviewing the relevant literature on the treatment of chronic functional constipation with acupuncture in the past 10 years, the author summarised and generalised from the aspects of regulating intestinal flora, regulating gastrointestinal dynamics, regulating neurotransmitter balance, and influencing intestinal nerves.

2. Pathogenesis of Chronic Functional Constipation

2.1 Altered Intestinal Flora

The intestinal microecosystem is an organic whole composed of the microbiota, the host and the intestinal environment, which are interdependent and constrained, and it is involved

in the regulation of human immune metabolism and anti-inflammatory and antioxidant pathways in order to maintain intestinal microecological balance. A growing body of research has shown that the gut microbiota plays a crucial role in gut health, and that the microbiota influences a wide range of pathophysiological activities in the host, and that building and maintaining a beneficial balance of gut flora is essential to ensure normal gut functioning [7]. It has been thoroughly researched that intestinal microecological dysregulation is the key mechanism of functional constipation, and the core essence of constipation is the dysfunction of intestinal flora structure and function [8]. More and more studies have shown that constipation patients have abnormal intestinal flora, and abnormal intestinal flora can aggravate constipation. Wang Fang [9] et al. studied the intestinal flora of patients with severe functional constipation and found that the number of normal bifidobacteria in patients with functional constipation was significantly lower than that of healthy controls, while the number of enterococci was significantly higher in patients, the number of fungi was significantly higher than that of healthy controls, and the number of *Candida albicans* and mycobacteria was significantly higher than that of healthy controls. these flora changes can easily lead to infections, weakened intestinal peristalsis and constipation. On the other hand, it will lead to an imbalance of intestinal flora, antagonising the growth of bifidobacteria and preventing them from performing their normal functions [9]. All of the above suggests that changes in intestinal flora are closely related to the development of functional constipation.

2.2 Morphological Changes in the Intestinal Tract

Morphological changes in the intestine of patients with chronic constipation are mainly characterised by altered intestinal motility, enteric nervous system (ENS) effects and abnormalities in Cajal mesenchymal cells.

2.2.1 Intestinal motility and ENS

Gastrointestinal smooth muscle as the final effector of gastrointestinal activity, its activity is uncoordinated, abnormal morphology can affect colonic peristalsis. In patients with functional constipation, alterations in colonic dynamics are mainly manifested by a decrease in the duration and number of colonic motions, and a significant decrease in the frequency and amplitude of pressure propagation waves in the colonic lumen. ENS innervates the activity of intestinal smooth muscle. Zhang Yan et al. found that the number of colonic ganglia in rats was significantly reduced by animal experiments, and the degenerative neuronal lesions were significant, so it was speculated that ENS dysfunction and the reduction of nerve conduction function caused the occurrence of STC [10].

2.2.2 Cajal mesenchymal cells

Cajal interstitial cell (ICC) is a type of non-neural interstitial cell in the gastrointestinal tract that is closely related to ENS. It was first discovered by Cajal, a Spanish neuroanatomist, and named after him. ICC is distributed in the intestinal interosseous muscle and is closely associated with intestinal wall interosseous smooth muscle cells and nerve endings. It mediates the transmission of ENS information and is the pacemaker of intestinal slow waves, which is important for intestinal motility. The clinical symptom of functional constipation, as shown in recent studies, is a significant decrease in the specific frequency as well as the amplitude of colonic propulsion. Changes in pressure in the colon, resulting in food residues stay too long, and can not be discharged at a normal rate, and enhance the non-propulsive peristalsis associated with accelerated intestinal absorption of water, so that the faeces are dehydrated and dry, so that it is difficult for the body to discharge [11]. It is hypothesised that STC patients have reduced colonic transport function while neurological alterations regulate intestinal activity [12]. Abnormal distribution of Cajal mesenchymal cells in the intestines and reduced secretion are also major causes of constipation, which may be one of the etiological factors of chronic functional constipation [13].

2.3 Altered Neurotransmitters in the Gut

The smooth muscles of the gut are innervated by the enteric nervous system (ENS), which includes postsynaptic innervation by excitatory and inhibitory neurons. Acetylcholine (ACh) has been identified as one of the physiological neurotransmitters of excitatory neurons, while substance P (P substance, SP), among others, also functions as an excitatory neurotransmitter. In addition, inhibitory motor neurons may be nitric oxide (NO), intestinal vascular polypeptide (VIP), and adenosine triphosphate (ATP), etc. [14] These neurotransmitters are closely related to mechanisms of electrophysiology, synaptic activity, and neural circuits that underlie neural activity in the gastrointestinal tract.

ACh is a widely studied excitatory neurotransmitter that regulates gastrointestinal motility by binding to M receptors within the intestinal wall. Several studies have found that in patients with chronic constipation, the maximum binding number of M receptors on the membranes of colonic smooth muscle cells is significantly reduced, leading to impaired colonic contraction and diastole, which in turn affects the

transport function of the colon. Du Lijuan [15] et al. observed that the abnormal distribution of VIP in the colonic interosseous plexus of rats with chronic constipation was associated with the development of chronic constipation. Furthermore, according to other scholars, we know that VIP acts mainly as a downward inhibitor and is not associated with colonic propulsive motility. Decreased levels of VIP lead to an increase in colonic non-propulsive motility, which in turn diminishes effective propulsive motility [16].

NO is one of the important inhibitory neurotransmitters in the ENS and plays a key role in the regulation of digestive tract dynamics. A study by Tan Li et al, showed that NOS expression was significantly enhanced and the number of positive cells increased in patients with chronic constipation. Abnormal expression of NOS leads to excessive NO production, and the excess NO causes the colon to be in a state of continuous inhibition, which leads to weakened intestinal peristalsis [17]. Thus, in patients with chronic constipation, levels of excitatory neurotransmitters are reduced and levels of inhibitory neurotransmitters are increased, which may lead to dysfunctional gastrointestinal motility. Studying the mechanism of action of intestinal neurotransmitters and modulating them is important for improving gastrointestinal motility function in patients with chronic constipation and developing related drugs.

3. Mechanism of Acupuncture in the Treatment of Chronic Functional Constipation

3.1 Acupuncture Regulates Intestinal Flora

A number of clinical trials [18][19] have confirmed that the use of acupoint acupuncture can significantly alter the ratio of beneficial to pathogenic bacteria in the digestive tract, inhibit the expression of inflammatory factors and thus achieve its therapeutic effect. The experiment of Sun Yiming [20] found that patients were subjected to acupuncture and moxibustion, respectively, and changes in the community structure of intestinal flora appeared in the two groups before and after the treatment, and the number of intestinal *Prevotella* spp. would be increased in patients with functional constipation after stroke through acupuncture treatment, while methanogenic bacteria decreased. Moxibustion will increase the number of SCFAs bacteria, *Bifidobacterium bifidum* and *Lactobacillus*, while decreasing the abundance of *Enterococcus*, *Enterobacteriaceae*, *Clostridium*. Experiments by Mingmin Xu [21] showed that acupuncture can effectively adjust intestinal flora metabolites and promote the balance of intestinal flora. In order to prove this point, they selected the "front-mu point" and "back-shu point" of rats with functional constipation and carried out acupuncture, and found that the number of beneficial bacteria was significantly increased, the number of harmful bacteria was significantly reduced, and the production and distribution of SCFAs, SLCFAs and 5-HT were also improved, which helped to enhance the vitality of the intestinal tract and effectively alleviate the symptoms of functional constipation. This helped to improve the intestinal vitality of the rats and effectively alleviated the symptoms of functional constipation. According to previous studies, acupuncture and moxibustion treatment helps to improve intestinal motility, regulate SCFAs metabolites and promote

intestinal microbial balance. For the current research on a large number of mechanisms, most scholars believe that acupuncture and moxibustion can affect the intestinal flora through the brain gut axis, and the brain gut axis forms a two-way interactive neuroendocrine immune network system with the intestinal tract through the central nervous system, the intestinal nervous system, etc., thereby affecting people's digestion and absorption. Therefore, current research shows that acupuncture and moxibustion can play a role in regulating intestinal microorganisms.

Gastrointestinal dysfunction is usually divided into two types: gastrointestinal motility hyperactivity or disorders. The "bidirectional regulation" effect of acupuncture can address this issue. Through acupuncture, people can increase the frequency and tension of intestinal fast waves, thereby enhancing the peristalsis ability of the intestine and promoting normal peristalsis of the large intestine. Sun Jianhua and his team found that electroacupuncture at the Tian Shu acupoint can help regulate the colonic transit function in rats with slow transit constipation, especially the abnormal slow wave rhythm of the colon [22]. Research by He Hongbo et al, found that this method helps to shorten colon transit time and improve intestinal transit efficiency [23]. In addition, Wang Lu utilized the autophagy of intestinal glial cells and the PI3K-AKT-m TOR signaling pathway to explore the regulatory mechanism of gastrointestinal transport in FC rats [24]. Other studies have shown that the phosphatidylinositol (PI3K) - protein kinase B (PKB, AKT) - rapamycin target protein (mTOR) channel is a ubiquitous mechanism that not only participates in protein composition, but also promotes cell growth and development, and regulates cell migration [25]. Therefore, after acupuncture and moxibustion treatment, the first black stool excretion time of FC mice is significantly reduced, and it will also increase the defecation rate of 8 hours, enhance the emptying rate of the stomach, speed up the advancement of the small intestine, and repair the intestinal tissue morphology. Through acupuncture and moxibustion, the expression of LC3 protein and mRNA was significantly increased, thereby activating autophagy of EGCs, enhancing gastrointestinal activity, and playing an anti FC effect. Researchers believe that the regulatory effect of EGCs on autophagy is largely due to the PI3K AKT mTOR signaling system.

3.2 Acupuncture and the Enteric Nervous System

3.2.1 Acupuncture regulates neurotransmitters

Researchers [26] have found that stimulating the intestines of model mice with electroacupuncture can effectively improve the expression of damaged cholinergic neurons (BDNF) and acetyltransferase in ENS, thereby improving symptoms of functional constipation. After the research of Sun Yanhui and others [27], they found that the positive expression of SP and VIP in the colon of STC rats decreased significantly, while acupuncture and warm acupuncture and moxibustion can effectively improve this situation, and warm acupuncture and moxibustion is more effective. Gao Yanhong et al [28], conducted a grouping experiment on patients with chronic transit constipation, and the results showed that the acupuncture group had better long-term treatment effects than the lactulose group. Both groups were able to increase plasma

MTL and SP levels, and reduce SS and VIP levels. Many studies [29][30] have shown that acupuncture and moxibustion can reduce the serum SS level of FC rats. It can be preliminarily speculated that acupuncture intervenes in the treatment of chronic functional constipation by affecting the balance of neurotransmitter levels. That is, the mechanism of acupuncture treatment for FC may be to maintain the balance of intestinal neurotransmitters by reducing the levels of inhibitory neurotransmitters such as SS and increasing the levels of excitatory neurotransmitters such as SP.

3.2.2 Acupuncture regulates Cajal interstitial cells

Through the exploration of Gao Fang [31] and other researchers, giving STC mice acupuncture and moxibustion treatment can significantly reduce the duration of the first defecation, and can increase the number of stool particles within 12 hours. At the same time, it can also enhance the expression level of ICC immunostaining positive cell bodies in mice with chronic constipation. Guo Hui and other scholars [32] have shown in experiments on STC model rats that the expression level of SCF gene significantly decreases, causing damage to the c-kit/SCF system. However, electroacupuncture at Tianshu can up regulate the gene expression of c-kit and SCF, which may be one of the principles of acupuncture and moxibustion in treating slow transit constipation. C-kit protein is a transmembrane glycoprotein specifically expressed on the Cajal interstitial cell membrane, which can interact with the ligand stem cell factor (SCF) to trigger a series of neural regulatory mechanisms. These mechanisms play an extremely important role in the growth, development, and morphological stability of ICC. According to the latest research results, overexpression of c-kit and SCF genes, as well as disruption of their corresponding neuronal transmission pathways, can have adverse effects on the structure and function of ICC. This conclusion suggests that the expression of c-kit protein can serve as a key regulatory mechanism during the treatment of STC [33]. Based on the above, it is speculated that the possible pathway of acupuncture treatment for STC is to upregulate the expression of c-kit protein and affect the regulation of Cajal interstitial cells, thereby affecting the ENS system.

4. Conclusion

In a word, acupuncture and moxibustion has achieved remarkable results in the treatment of functional constipation. Its principle of action can be summarized as: improving the proportion of intestinal flora, regulating the secretion of neurotransmitters, and affecting the regulation of interstitial cells of Cajal. In recent years, the exploration of changes in neural, biochemical mediators, and electromyographic activity has provided important evidence for the mechanism research of such diseases, and these changes are closely related to the changes in the "brain gut axis" [34]. Acupuncture can change the operation of the brain gut axis, thus changing the operating state of the nervous system, which is also the core principle of acupuncture and moxibustion treatment. In addition, with the popularization of the "biopsychosocial" medical model, more and more recent studies have studied functional constipation as a psychosomatic disease. However, the specific mechanism of

functional constipation as a psychosomatic disease is not yet fully understood and deserves further research.

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