Acupuncture and Herbal Medicine

OPEN

The role of acupuncture on the autonomic nervous system in irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by recurrent abdominal pain, bloating, and irregular bowel movements with complex pathogenesis. Due to its high prevalence and reoccurring symptoms, it seriously impacts patients' quality of life. One of the causes of IBS is turbulence of gastrointestinal motility and intestinal secretion due to dysfunction of the autonomic nervous system (ANS), which the includes the sympathetic nervous system, parasympathetic nervous system, and enteric nervous system. Current research has proven that acupuncture, a traditional Chinese therapy, is useful and effective for treating IBS. The ANS is a key pathway for bidirectional information transmission between the gastrointestinal tract and the central nervous system, which plays an important role in IBS treatment with acupuncture. Research on the mechanisms of acupuncture for IBS is receiving more attention, and the use of contemporary methods has made significant progress. Evidence suggests that acupuncture may mitigate the negative consequences of IBS, as seen by reduced inflammatory signaling, neurotransmitter levels in the colon and central neural tissues, and balanced gut flora. We review and discuss acupuncture's possible mechanisms of action for IBS treatment *via* the ANS, including modulation of gastrointestinal motility, improvement of visceral hypersensitivity, and innervation of the gut-brain-microbiota axis. Our review demonstrates the available evidence for acupuncture treatment of IBS in clinical settings; however, we also observe that the relationship between the ANS and the gut-brain-microbiota axis is unclear, and further research is needed.

Keywords: Acupuncture, Autonomic nervous system, Gut-brain-microbiota axis, Gut motility, Irritable bowel syndrome, Visceral hypersensitivity

Graphical abstract: http://links.lww.com/AHM/A57.

Introduction

Irritable bowel syndrome (IBS) is a globally prevalent chronic functional bowel disease that seriously affects patients' quality of life and increases the economic burden on society. The incidence of the disease has increased recently, with a global prevalence of about 11.2%[1]. IBS is mainly characterized by recurrent abdominal pain or bloating and irregular stools, and changes in defecation habits, accompanied by abnormal emotional performance[1], which is a typical clinical gastrointestinal physical and mental disorder. According to Rome IV diagnostic criteria[2], IBS can be divided into IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and IBS with unclassifiable bowel habits (IBS-U)[3]. IBS is a symptom cluster caused by a variety of conditions[4], including peripheral stress, affective disorders, and poor diet. The main pathological factors are abnormal gastrointestinal motility and altered visceral sensitivity, inflammation and gut-brain axis dysregulation, and somatic and psychiatric comorbidities[4].

Presently, drugs are primarily employed to treat symptoms rather than the root causes of IBS. Additionally, short-term drug use is frequently ineffective, whereas long-term use has negative side effects[5]. As an important part of traditional Chinese medicine, acupuncture has been recognized by the World Health Organization as a suitable treatment technique for at least 20 diseases and has been widely used in the treatment of functional bowel disorders. Studies have shown that compared with conventional Western medicine, acupuncture has a definite effect on IBS, which can improve the clinical symptoms of patients with IBS, such as abdominal pain, diarrhea, and abdominal distension, without noticeable adverse reactions[6], and improve their quality of life[7]. Additionally, acupuncture therapy effectively controls key IBS-related risk factors such as anxiety, aggressive behavior, food restrictions, and social responsiveness[8].

The autonomic nervous system (ANS) plays an important role in maintaining the body's cardiovascular system, gastrointestinal tract, and temperature homeostasis. It is traditionally composed of two parts, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The two sub-systems are dominated by the cerebral cortex and the hypothalamus,

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Acupuncture and Herbal Medicine (2023) 3:2

Received 8 October 2022 / Accepted 9 March 2023

http://dx.doi.org/10.1097/HM9.0000000000000063

which both antagonistically and coordinately regulate the physiological activities of organs[9]. The ANS is mainly distributed to the viscera, the cardiovascular system, and the glands. The central part is in the brain and spinal cord. The peripheral part includes visceral motor fibers and visceral sensory fibers, which constitute the visceral motor nerve and visceral sensory nerve, respectively.

Moreover, the fundamental role of the enteric nervous system (ENS), which is a subset of the ANS[10], is to govern physiological processes and maintain homeostasis. It has independent regulatory effects on gastrointestinal motility, secretion, and blood supply, and functional gastrointestinal disorders are closely related to intestinal neuromodulation of gastrointestinal dysfunction[11]. As a result, an abnormal ANS is a significant pathophysiology that causes dysfunctional intestinal secretion and motility. Current evidence shows that ANS disorders are closely related to IBS occurrence[12–13]. Furthermore, acupuncture stimulation with *de-qi* sensations has been demonstrated in human neuroimaging investigations to regulate autonomic nervous activity[14]. As acupuncture's effectiveness has been established, studies have now turned to understanding how it works. In this article, we review the relationship between IBS and ANS, as well as how acupuncture can treat IBS through the ANS.

We searched the EMBASE, PubMed, Chinese BioMedical Literature Database, China National Knowledge Infrastructure, Chinese Scientific Journal Database (VIP database), and Wanfang Database from their inception to December 1, 2022, in both Chinese and English. The search terms included intervention methods and diseases: (acupuncture OR electroacupuncture OR manual acupuncture OR needle) AND (irritable bowel syndrome OR IBS). The corresponding search words were employed in the Chinese databases.

The ANS status in IBS

The ANS is widely distributed, involves multiple regions of the nervous system, and is dominated by central neurons. Autonomic nerves can regulate the functional activities of internal organs and regulate the homeostasis of intestinal functions, including gastrointestinal motility and secretion of digestive juices. Intense stimulation of the gastrointestinal tract elicits regional responses that transmit information to the central nervous system (CNS) through the splanchnic and autonomic pathways to form a comprehensive behavioral and physiological response. The ANS plays an important role in this pathway. Moreover, the lower brainstem in the central ANS is also involved in controlling gastrointestinal functions. Patients with IBS experience severe autonomic dysfunction, which is directly tied to their physical symptoms and psychosocial aspects. Conclusively, the ANS is involved in the regulation of gastrointestinal motility, secretion, and immune function[15], and the ANS innervating the gastrointestinal tract is a key pathway for bidirectional information transmission between the gastrointestinal tract and the CNS[16], which explains the close association of IBS with ANS.

Changes in the SNS and PNS in IBS

Sympathetic and parasympathetic nerves have antagonistic effects; sympathetic nerves can slow down the heartbeat and strengthen gastrointestinal motility, whereas parasympathetic nerves can increase gastrointestinal activity, the secretion of digestive glands, and promote urine excretion. Moreover, 75% of the parasympathetic nerves are those of the vagus nerve. Decreased vagal activity or increased sympathetic activity is often associated with gastrointestinal motility.

Autonomic dysfunction usually manifests in IBS as low vagal tone and increased sympathetic drive. In the assessment of digestive and cardiac autonomic function in patients with IBS, abnormal autonomic reflexes may contribute to gastrointestinal motility disturbances. Moreover, patients with IBS exhibit increased sympathetic activity and decreased parasympathetic activity, which are both directly associated with altered autonomic responses[17]. In addition, they have greater parasympathetic withdrawal after eating[18]. Consistent with this study, colonic motility increased and vagal activity decreased in patients with IBS after eating, which may be closely related to the development of postprandial symptoms[13]. To study the effect of anticholinergic drugs on the colon of patients with IBS after a standard diet, Sullivan et al. discovered that colonic motor activity was abnormally prolonged in patients with IBS after meals, and anti-cholinergic drugs reduced the duration and degree of abnormal colonic reaction[19]. Consistent with most studies, patients with IBS showed increased SNS activity and decreased PNS activity compared with healthy individuals[20–21].

According to clinical investigations, IBS is more common in women and frequently manifests as non-painful gastrointestinal symptoms, constipation, and physical discomfort[22]. In clinical studies, parasympathetic activity was significantly increased in women with IBS-D compared with the IBS-C and IBS-M groups and was associated with sleep cycles[23]. Conversely, in men, SNS activity is high, while PNS activity is low[17]. Among healthy individuals, men have significantly increased vagal activity and greater responsiveness[24]. Sex variations occur among patients with IBS in terms of the central response to visceral stimulation and medication therapy[25], which raises the possibility that the ANS response varies between male and female patients with IBS. In addition, the psychological state is closely related to the feedback of the ANS. The physiological response caused by emotion is realized through the ANS and the endocrine system, and the endocrine system is dominated by the ANS. Compared with women with general IBS symptoms, parasympathetic nerve activity, and tone were significantly reduced among women with IBS and anxiety or depression[26]. Conclusively, patients with IBS often show increased sympathetic excitability, especially in the vagus nerve, whereas parasympathetic activity is decreased. This phenomenon is often associated with diet, sex, and mood.

Changes in the ENS with IBS

The ENS comprises several neurons embedded in the gastrointestinal wall, including primary afferent neurons,

interneurons, and motor neurons, which are mainly involved in gastrointestinal motility and mucosal transport, and regulate immunity and endocrine function. The ENS is relatively independent of the CNS, which plays an important role in integrating and regulating the function of the gastrointestinal system. Li et al.[27] used a heterotypic chronic and acute stress (CAS) rat model to investigate whether the effects of IBS on the gastrointestinal tract are produced through the ENS and observed that the intestinal motility of the CAS rats accelerated and the number of motor neurons increased, suggesting that changes in enteric neurons are one of the causes of IBS symptoms.

Neurotransmitters are chemicals that transmit information between neurons or between neurons and effector cells. Studies have demonstrated that neurotransmitters such as 5-hydroxytryptamine (5-HT), transient receptor potential vanilloid type 1 (TRPV1), and brain-derived neurotrophic factor (BDNF) in the ENS can promote secretion in the gastrointestinal tract, whereas neuropeptide Y (NPY) and calcitonin gene-related peptide (CGRP) have inhibitory effects[28]. As a brain-gut peptide closely related to gastrointestinal activity, 5-HT is produced from chromaffin cells in the intestine upon stimulation in the intestinal lumen and binds to receptors to induce enteric nerve reflexes[29]. Intestinal motility and mood are affected by 5-HT through binding to particular receptors in the colon and brain tissue. The study found that the level of 5-HT is increased and intestinal mucosal barrier damage is common in IBS, manifested as a partial reduction of tight junction proteins[30]. Moreover, as a membrane protein, TRPV1 is the most representative and studied nociceptor in visceral hypersensitivity. TRPV1 is highly expressed in the gastrointestinal tract in peripheral sensory neurons and intestinal neurons. Several researchers have demonstrated that high expression of TRPV1 in the gut is associated with the pathogenesis of visceral hypersensitivity in IBS[5,31–32]. In addition, BDNF is a generalized peptide hormone, and its abnormal elevation can lead to visceral hypersensitivity and abnormal intestinal motility. It can mediate visceral sensitivity and participate in the pathogenesis of IBS by promoting the growth of sensory nerves[33]. NPY has an important role in the ENS; it can participate in the secretion and absorption of fluids in the gastrointestinal tract by combining with the peripheral choline acetyltransferase in the intestinal sub-mucosal ganglia, and the decrease in NPY levels may lead to diarrhea occurrence in IBS[34]. CGRP has a protective impact on the gastrointestinal mucosa and is mostly found in the afferent fibers of the vagus, splanchnic nerves, and the intramural nerve plexus of the gastrointestinal tract. CGPR is currently recognized as a neuroactive substance closely related to nociceptive information transmission and is one of the causes of visceral hypersensitivity in IBS[35]. The findings above demonstrate that the changes in neurotransmitters in the ENS are one of the important pathological factors of IBS.

Clinical study on acupuncture treatment of IBS

As a traditional Chinese medicine external therapy, acupuncture works by activating acupoints to clear obstructions in the meridians and collaterals, control *qi* and blood flow, promote health, and drive pathogens out of the body. By activating acupoints, which are not only the locations where the *qi* of meridians is infused onto the body's surface but also the locations where illnesses reflect on the body's surface, acupuncture treats the body as a holistic system. Acupuncture and technology are combined through the use of electroacupuncture (EA) in contemporary society. To improve stimulation and clinical efficacy following acupuncture, it mostly involves supplying current to the location of the needle. Acupuncture and EA are widely applied in clinical practice to treat IBS[36]. The effects of EA and acupuncture on IBS are different, which may be caused by stimulation methods, intensity, and body response.

This disease's vital traditional Chinese medicine pathogenesis is spleen deficiency and liver depression. The condition affects the gut and is linked to the heart and brain. Therefore, soothing liver and strengthening spleen is the focus of the treatment of this disease. In the treatment of IBS with acupuncture, the commonly used meridians include the Stomach Meridian Foot-Yangming, Spleen Meridian of Foot-Taiyin, Liver Meridian of Foot-Jueyin, Governor Vessel, and Conception Vessel. The frequently used acupoints include Baihui (GV20), Yintang (GV29), Sanyinjiao (SP6), Taichong (LR3), Dachangshu (BL25), Zhongwan (CV12), Tianshu (ST25), Zusanli (ST36), and Shangjuxu (ST37)[37]. In comparative efficacy trials in China, patients reported greater benefits from acupuncture than pharmacological therapies. Extensive experience has been amassed for the use of acupuncture, which has improved effectiveness, and has the potential for future study, with its ability to relieve symptoms, improve quality of life and reduce healthcare burden. A Korean study confirmed that acupuncture could improve intestinal symptoms such as loose stool, bloating, abdominal discomfort, and abdominal pain in patients with IBS[38]. In addition, previous studies have reported that acupuncture may be more effective than polyethylene glycol and pinaverium bromide, with effects lasting up to 12 weeks[39]. Additionally, acupuncture can reduce IBS symptom severity scores and has an additional benefit over usual care alone. Therefore, it should be considered a therapy option alongside other evidenced-based treatments.

Acupuncture for IBS Treatment through the ANS

Acupuncture, an appropriate technique in traditional Chinese medicine, has been widely used to regulate neurological diseases, such as pain syndromes. It modulates the function of internal organs by activating visceral reflexes and autonomic nerves through stimulation of the body surface[40]. There is evidence from research on acupuncture practice which shows that acupuncture and ANS function are tightly associated[41]. The mechanism of action of acupuncture for IBS treatment is mainly by ANS regulation to improve gastrointestinal motility, visceral hypersensitivity, and the brain-gut axis[42].

Acupuncture modulates gastrointestinal motility and visceral sensitivity in IBS via the ANS

Acupuncture can regulate the autonomic nerves through the spinal cord, mainly by the body surface-autonomic reflex. The route is determined by the autonomic

innervation properties of the organ and the spinal cord segment at the stimulation site. The integrity of the sympathetic nerve is required for acupuncture to regulate the organs of the same segment, whereas the integrity of the vagus nerve is required for the stimulation of acupoints of different segments to produce therapeutic effects. Acupuncture regulates gastrointestinal motility and visceral sensitivity through the dual innervation of sympathetic and parasympathetic nerves. Studies have shown that acupuncture can reduce gastric acid secretion[43] and inhibit prolonged gastric emptying after vagotomy[44]. In IBS, acupuncture alters visceral sensation and motility by stimulating the somatic nervous system and vagus nerve[45–46]. In IBS rats, EA at ST25 alone can reduce visceral hypersensitivity and return the colon's slow-wave frequency and rhythm to normal, indicating that acupuncture may work through the ANS[47].

The myenteric plexus mainly controls intestinal motility, and the sub-mucosal plexus mainly controls the secretion and absorption of intestinal fluids in the ENS. Interstitial cells of Cajal are the mediators of the ENS in controlling gastrointestinal smooth muscle movement. Acupuncture can regulate the gastrointestinal function of IBS by inhibiting the expression of the c-kit receptor, a marker of Cajal cells. Furthermore, evidence suggests that visceral hyperalgesia in IBS is mainly caused by the abnormality of intestinal sensory neurons[48], and acupuncture can increase the pain threshold and reduce visceral hyperalgesia[49–50]. Various neurotransmitters have been identified in enteric neurons. Acupuncture can improve gastrointestinal motility and visceral hypersensitivity by regulating neurotransmitters. For example, EA at ST25 and ST37 points can improve the pain threshold in IBS rats with chronic visceral hypersensitivity and reduce the abnormally increased 5-HT concentration in the model colon tissue[51]. Research also shows that EA at ST36 and ST37 may alleviate colorectal hypersensitivity by regulating TRPV1[52]. Acupuncture can help patients with IBS by lowering the level of CGRP in their blood, thereby improving chronic anxiety and despair. In addition, research suggests that EA may improve visceral sensitivity in IBS rats by reducing colonic BDNF, 5-HT, and CGRP expression and increasing NPY levels[8,53].

In summary, acupuncture can innervate sympathetic and parasympathetic nerves, regulate autonomic balance function, and improve gastrointestinal motility and visceral sensitivity in IBS. Furthermore, acupuncture can also regulate the release of neurotransmitters in the intestinal tract, block the conduction pathway of external pressure stimulation, reduce the production of visceral pain stimulators, and aid the overall improvement of IBS symptoms, including mental state and gastrointestinal function (Figure 1).

Acupuncture modulates the gut-brain-microbiota axis in IBS via the ANS

The CNS, ANS, hypothalamic-pituitary-adrenal axis (HPA), and ENS are the basic parts of the brain-gut axis, which regulates bidirectional signal communication between the nervous system and the gastrointestinal tract. The brain-gut axis regulates immune, endocrine, and neural pathways in stress response processes. The CNS controls the signals from the vagus nerve and spinal cord to reach the intestinal tract and regulates intestinal flora homeostasis. This process will eventually affect the brain-gut axis[54–55] and, thus, the complex system of gut-brain-microbiota axis interactions. IBS symptoms activate immunity in the brain *via* vagal afferent fibers and the HPA[56–57].

Based on the findings from studies on diseases involving abnormalities of the gut-brain axis and gut microbiome, acupuncture can improve gut microbiota balance in IBS[58–59]. A meta-analysis has shown that patients with IBS have reduced types and numbers of beneficial bacteria and increased levels of harmful bacteria

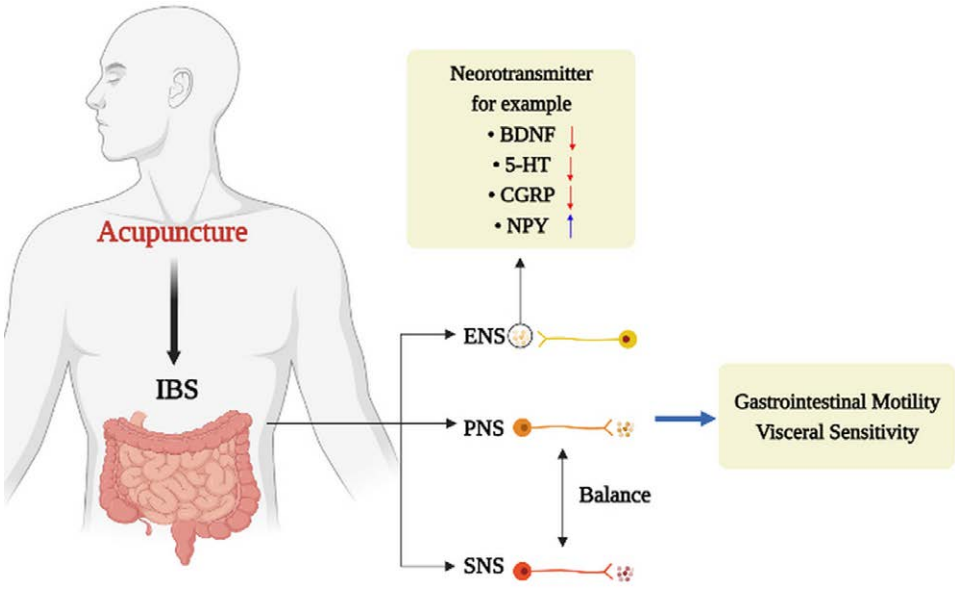

Figure 1. Acupuncture improves gastrointestinal motility and visceral sensitivity by modulating the autonomic nervous system. 5-HT: 5-hydroxytryptamine; BDNF: brain-derived neurotrophic factor; CGRP: calcitonin gene-related peptide; ENS: enteric nervous system; IBS: irritable bowel syndrome; NPY: neuropeptide Y; PNS: parasympathetic nervous system; SNS: sympathetic nervous system.

in their intestines compared with healthy people[60]. Acupuncture can change the structure and diversity of intestinal flora, reduce the content of short-chain fatty acids in feces, and improve the symptoms of diarrhea and abdominal pain in IBS[61]. In basic research, acupuncture reduced substance P (SP), vasoactive intestinal peptide (VIP) in the colon and cecum, CRH in the hypothalamus, 5-HT and CGRP in the spinal cord, and up-regulated NPY in the spinal cord and hypothalamus in IBS rats. In addition, acupuncture improved the gut-brain axis and gut microbiota changes by inhibiting mucous mast cell activation and neuropeptide over-secretion, reducing visceral pain sensitivity, and modulating ANS dysfunction in IBS rats[8,62–63]. In clinical studies, acupuncture can activate the right insula, the medial nucleus, and the pulvinar thalamus, and reduce SP and VIP in the colonic mucosa, and 5-HT in the sigmoid colon tissue in patients with IBS. It can also regulate the ANS, treat visceral pain, improve mood, and restore the balance of brain-gut axis function in patients with IBS[64–66]. In addition, acupuncture stabilizes the mechanical barrier of the intestinal mucosa by improving abnormally increased mucosal permeability and regulating the expression of tight junction proteins, thereby treating emotional-psychological disorders and restoring vagal-sympathetic balance.

In conclusion, acupuncture can alter the type of intestinal flora, improve intestinal mucosal permeability, restore the balance of the ANS, and ultimately regulate the gut-brain-microbiota axis by modulating the functional state of brain areas and neurotransmitters of the ENS (Figure 2).

Summary and prospect

Acupuncture is effective at regulating the ANS, particularly the digestive system. The characteristics of acupuncture for IBS treatment include the diversity of acupoints, EA as the main intervention. And the effect pathway is mainly evidenced in animal experiments, and the effect characteristics are specific and related to the stimulation method[67]. However, the National Institutes of Health has recently launched the Stimulating Peripheral Activity to Relieve Condition (SPARC) program, which aims to explore the clear connection between peripheral nerves and internal organs[68] and to directly stimulate peripheral nerves to treat certain diseases that are not well-received by conventional treatments. Although the theoretical system, mechanism of action, and stimulation methods of the SPARC program are different, the stimulation sites and nerve conduction mechanisms are similar to acupuncture. In addition, advanced neuroscience technology is integrated into the SPARC program, which provides ideas for the study of acupuncture to stimulate the ANS in the treatment of gastrointestinal diseases.

The selection of acupoints is crucial when acupuncture is used to treat diseases, and the effect of various acupoints on autonomic nerves differs. For example, EA at ST36 can drive the vagal-adrenal axis but not at ST25[69]. Although acupuncture can treat IBS *via* the ANS, the exact mechanism of action of acupoints is unclear. Furthermore, systemic therapy is frequently chosen based on the clinical situation, including the improvement of somatic symptoms and psychological disorders. However, it is difficult for acupuncture to exert a systematic therapeutic effect on the animal model of IBS. Thus, we speculate that acupuncture regulation of the ANS may involve diverse links and targets.

The existing research cannot fully explain the mechanism of acupuncture for IBS treatment from the aspect of the ANS. Additionally, the effects of acupuncture on the gut-brain-microbiota axis in patients with IBS *via* the ANS are also understudied; there are still many unanswered questions in this pathway, including

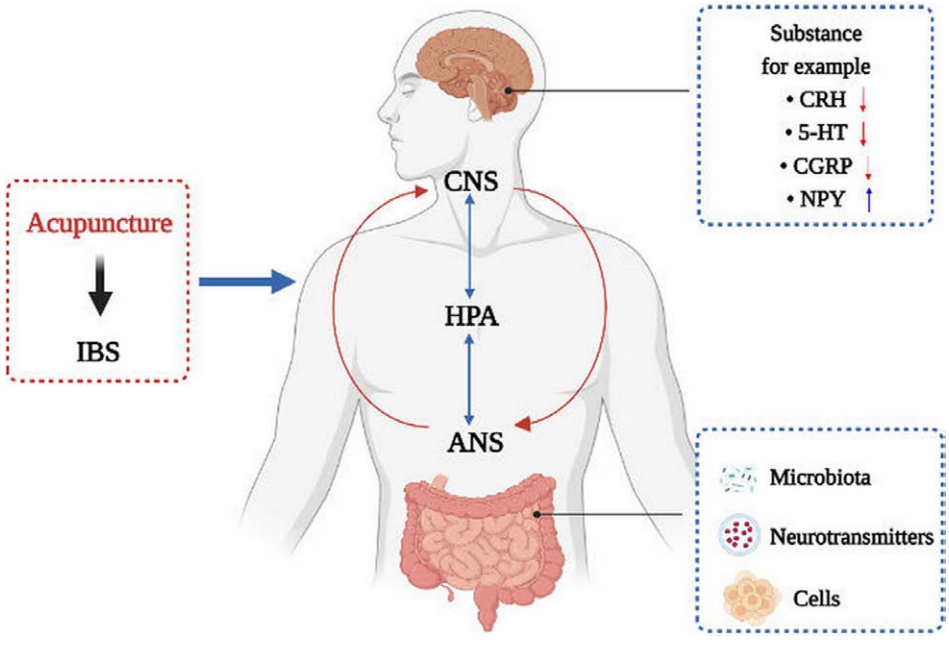

Figure 2. Acupuncture regulates the brain-gut axis through the autonomic nervous system. 5-HT: 5-hydroxytryptamine; ANS: autonomic nervous system; CGRP: calcitonin gene-related peptide; CNS: central nervous system; CRH: corticotropin-releasing hormone; HPA: hypothalamic-pituitary-adrenal axis; IBS: irritable bowel syndrome; NPY: neuropeptide Y.

the relationship between gut microbes and autonomic nerves. Exploring the neuro-visceral system greatly benefits from research on the effects, characteristics, and acupuncture pathways on the ANS. Therefore, further research is needed on how acupuncture modulates the ANS to improve IBS symptoms.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This work was supported by the National Key R&D Program; the Key Project of Modern Research in Traditional Chinese Medicine (2019YFC1712103).

Author contributions

This study was conceived by Luqiang Sun and Junpeng Yao. Data were collected by Fangli Luo, Shuai Chen, and Di Qin. The content was modified by Yujun Hou, Lu Wang, and Ying Li. The first draft of the article was prepared by Luqiang Sun. All authors approved the final article.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

We are really grateful to Qianhua Zheng, Haiyan Wang, and Jie Chen for their insightful conversation.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Sun LQ, Yao JP, Luo FL, Chen S, Qin D, Hou YJ, Wang L, Li Y. The role of acupuncture on the autonomic nervous system in irritable bowel syndrome. Acupunct Herb Med 2023;3(2):76–82. doi: 10.1097/HM9.0000000000000063