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Review on Research Progress of Irritable Bowel Syndrome with Traditional Chinese Medicine Based on Signaling Pathways

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Abstract: *Irritable bowel syndrome (IBS) is one of the common diseases and frequently-occurring diseases of digestive system. Its clinical manifestations are mainly characterized by abdominal pain and changes in bowel habits. And it is difficult to cure it. The mainstays of treatments include diet, exercise, symptomatic treatment drugs and psychological intervention. These methods have good therapeutic effect but easy recurrence. Traditional Chinese medicine (TCM) emphasizes syndrome differentiation and treatment based on the etiology and pathogenesis, with good curative effect and limited side effects, so it has significant advantages in clinical practice. Understanding the signaling pathways associated with IBS is important for studying the pathogenesis of IBS in the future and for finding potential therapeutic targets. Taking the pathogenesis of irritable bowel syndrome as a starting point, this review introduces the modulation of IBS-related signalling pathways by TCM, aiming to provide in-depth studies on TCM treatment of IBS and inspire new research ideas.*

Keywords: *Traditional Chinese medicine, Irritable bowel syndrome, Signaling pathways, Research progress, Mechanism*

Irritable bowel syndrome (IBS) is a functional bowel disease with recurrent abdominal pain, abnormal defecation or change in bowel habit as the main symptom, or with gastrointestinal symptoms such as abdominal bloating and gastrointestinal gas[1]. Currently, it is believed that the main pathogenesis of IBS is visceral hypersensitivity, abnormal brain-gut axis interaction, and low-grade inflammation of the intestinal tract, but its specific pathogenesis has not yet been clarified. Clinically, IBS is mainly intervened by diet, exercise, symptomatic therapeutic drugs and psychological interventions, but there is no uniform standard, and the overall treatment effect is fair but easy to relapse. Therefore, research and clarification of the pathways of IBS can help guide clinical diagnosis and treatment. The pathways of TCM in treating IBS are numerous, and it can improve the symptoms and quality of life of patients through multi-pathway and multi-targeted treatment of IBS. However, there are fewer articles summarising the signalling pathways related to IBS regulated by TCM with the pathogenesis of IBS as the starting point, therefore, this review summarises the signalling pathways of IBS regulated by TCM.

1. Chinese medicine intervention in IBS-related signalling pathways

1.1 Toll-like receptor 4/nuclear factor κB signalling pathway

Toll-like receptor 4 (TLR4)/nuclear factor κB (NF-κB) signalling pathway regulates the transcription of inflammation-related genes and is at the centre of immune regulation[2].Toll-like receptor not only binds specifically to the κB sequence of Ig protein genes to regulate T and B cell maturation and activation, but also regulates the transcription of inflammatory factors and cytokines, and participates in various inflammatory processes.IBS patients' intestinal mucosal biopsies showed low inflammatory responses, while TLR4/NF-κB signaling pathways were found in IBS patients. and activation, but also regulates the transcription of inflammatory factors and cytokines, and participates in various inflammatory processes.Intestinal mucosal biopsies of IBS patients show low inflammatory responses, and the TLR4/NF-κB signalling pathway can disrupt the balance between pro-inflammatory and anti-inflammatory factors, thus affecting the prognosis of IBS[3].The TLR4/NF-κB signalling

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pathway is involved not only in intestinal inflammatory responses but also in IBS visceral hypersensitivity.

Chu Haoran[4] and others demonstrated that moxibustion of "Tianshu" and "Shangjuxu" can effectively reduce the inflammatory response of rat colon mucosa. Zhao et al.[5] showed that Qinghua antidiarrheal formula could inhibit the TLR4/NF-κB signalling pathway, thus maintaining the balance between pro-inflammatory and anti-inflammatory factors. Wu Jing[6] et al. showed that Dajianzhong Tang could inhibit key molecules such as substance P(SP), TLR4, and NF-κB (p65), and then achieve the purpose of analgesic effect on visceral pain rats in IBS model.

1.2 5-hydroxytryptamine signalling pathway

5-Hydroxytryptamine (5-HT) is a brain-gut peptide synthesised and released by enteroendocrine cells in the gastrointestinal mucosa, which can affect gastrointestinal motility and visceral sensitivity by regulating gastrointestinal motility and secretion[7]. It has been shown that the pain threshold for rectal dilatation is significantly lower in IBS patients compared to controls[8]. The development of psychogastroenterology has led researchers to recognise brain-gut axis dysfunction as one of the major pathogenic mechanisms of IBS[9], with the involvement of 5-HT as a neuromodulatory peptide that controls brain-gut axis neurotransmission.

Zhang Wei[10] et al. found that the addition and subtraction of the elicitor drug Fang Feng from the Essentials of Painful Diarrhoea Formula could improve visceral pain sensitivity in rats. This experiment also proved that Fangfeng also has the effect of enhancing the regulation of 5-HT signalling pathway by the Essentials of Pain and Diarrhoea formula. An intestinal soup can regulate the visceral hypersensitivity of IBS-D patients by decreasing 5-HT in the serum of patients and achieve the relief of abdominal pain and diarrhoea in patients[11]. Liang Ruifeng et al.[12] found that Painful Diarrhoea Essentials can improve the symptoms of IBS rats by regulating the content of brain-gut peptides, such as 5-HT and SP, in different target points of the brain-gut axis. Warm stomach and intestinal regulating granules can down-regulate the expression of brain and intestinal peptides (5-HT, SP) in the hypothalamus and intestinal mucosa, and regulate the balance of brain-intestinal interactions, thus improving the gastrointestinal peristaltic disorders and sensory abnormalities[13].

1.3 Transient receptor potential vanilloid 1 signalling pathway

The transient receptor potential channel vanilloid 1 (TRPV1) acts as a homotetramer whose activation is associated with chronic inflammatory pain and peripheral neuropathy[14]. Sensitisation and up-regulation of TRPV1 sensitises afferent nerves, leading to visceral hypersensitivity[15].When TRPV1 is sensitised, extracellular Ca2+ and Na+ are inwardly flowing, releasing gastrointestinal peptides such as calcitonin gene-related peptide (CGRP) and SP, leading to gastrointestinal hypersensitivity reactions[16].

Buckwheat extract was found to inhibit the peak TRPV1 current in dorsal root neurons of the lumbosacral spinal cord in IBS rats to improve nociceptive hypersensitivity in model rats[17]. Han Yafei et al.[18] experimentally demonstrated that Painful Diarrhoea and Intestinal Formula could reduce visceral hypersensitivity in IBS rats by decreasing colonic nerve growth factor and TRPV1 protein expression. Fang Jiansong et al.[19] found that liver-sparing and spleen-strengthening formula could down-regulate the sensitisation of TRPV1, thereby reducing visceral hypersensitivity, regulating gastrointestinal motility and alleviating IBS symptoms in IBS rats.

1.4 Mitogen-activated protein kinase signalling pathway

The mitogen-activated protein kinase (MAPK) signalling pathway has three subfamilies: c-Jun amino-terminal kinase 1/2, extracellular signal-regulated kinase (ERK) and p38, which are involved in the mechanisms of IBS such as low-grade inflammation in the intestine and visceral hypersensitivity. mechanisms of IBS development such as intestinal low-grade inflammation as well as visceral hypersensitivity. p38 MAPK cascade, when activated, plays an important role in cellular responses such as inflammation, cell proliferation and differentiation, and apoptosis, which induces intestinal low-grade inflammation. ERKs are important signal transducing protein kinases and activation of ERK1/2 is particularly critical for the regulation of visceral hypersensitivity[20]. p38 MAPK signalling pathway also has an important role in gastrointestinal dyskinesia and pain perception in the body. One study has identified the MAPK/ERK signalling pathway as one of the signalling pathways involved in

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brain-gut interaction in IBS[21].

Guo Junxiong et al.[22] demonstrated that the pain and diarrhoea formula could inhibit the activation of the p38 MAPK signalling pathway and reduce the inflammatory response. It was found that the combination of acupuncture Hejiao and Qiaolu Essentials could inhibit the abnormal activation of MAPK/ERK signalling pathway, significantly improve the anxiety and depression status of patients with IBS-D, and alleviate the clinical symptoms of the patients[23]. Sijunzi Tang combined with Siwei San can regulate the changes in the MAPK/ERK signalling pathway mediated by abnormal levels of brain gut peptides such as 5-HT and SP, thus improving peripheral sensitisation and central sensitisation[24].

1.5 Stem cell factor/tyrosine kinase receptor signalling pathway

The stem cell factor (SCF)/tyrosine kinase receptor (c-kit) signalling pathway, consisting of SCF and its cognate receptor c-Kit, is a major regulator of the survival and function of a wide range of neural crest-derived cells, mainly those involved in visceral sensing, smooth muscle contraction and inflammation. Alterations in the SCF/c-Kit signalling pathway lead to disturbances in the neuroendocrine-immune network, providing an explanation for the visceral hypersensitivity, abnormal intestinal contractile strength and low-grade inflammation in IBS.

Cangzhu oil may alleviate symptoms in IBS-D model rats by inhibiting SCF/c-kit signalling, thereby reducing the expression of inflammatory factors[25]. Li Hui et al.[26] found that quenching wind and transforming dampness formula could inhibit the overexpression of SCF/c-Kit signalling pathway and reduce visceral hypersensitivity in IBS rats. Rui et al.[27] showed that Painful Diarrhoea Essential Formula could improve the symptoms of diarrhoea in rats.

1.6 Other related signalling pathways

1.6.1 Janus kinase/signal transducer and activator of transcription signalling pathway

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signalling pathway is involved in many cellular processes, including cell division, cell death and regulation of immune function.JAK2/STAT3 is an important pathway that mediates apoptosis and inflammatory signal transduction in cells. JAK2/STAT3 is an important pathway mediating apoptosis and inflammatory signalling. Some studies have confirmed that the development of visceral hypersensitivity is closely related to the activation of the JAK /STAT signalling pathway[28]. Lai Lei[29] found that Painful Diarrhoea Essentials could inhibit the JAK/STAT signalling pathway involved in the intestinal inflammatory response to alleviate the visceral hypersensitivity of IBS through her study.

1.6.2 Brain-derived neurotrophic factor/tyrosine kinase receptor B signalling pathway

Brain-derived neurotrophic factor (BDNF) affects enteric nervous system development and has a nociceptive and sensitising effect. Tyrosine kinase receptor B (TrkB), a functional receptor for BDNF, plays an important role in cell signalling. Pan Xiaoou[30] et al. experimentally confirmed that dendrobine could improve the symptoms of pain and diarrhoea in IBS model mice by reducing the release of 5-HT and SP, inhibiting the expression of BDNF, and decreasing the sensitivity of viscera.

1.6.3 Phosphatidylinositol 3-kinase/protein kinase B signalling pathway

Phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) has an important role in the pathogenesis of tumours, inflammation and immune diseases. It has been found that the PI3K/AKT signalling pathway induces cellular autophagy and is involved in intestinal mucosal barrier changes[31]. Xia Li Xian et al.[32] found that Painful Diarrhoea Essentials may reduce the occurrence of cellular autophagy and restore the intestinal mucosal barrier by inhibiting the PI3K/AKT signalling pathway, thus reducing visceral hypersensitivity.

2. Interconnections between pathways

The development of IBS is quite complex, and its specific pathogenesis has not been fully clarified. The above signalling pathways do not play a single role in each other, but rather interact with each other to produce a cascade response that is amplified step by step, thus affecting the biological process. Therefore, TCM can intervene in multiple signalling pathways and regulate the expression of different proteins to prevent and treat IBS.

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When TLR4 is activated by stimulation, TLR4 regulates the transcription of cytokine SCF, and the SCF/ c-kit signalling pathway activates its downstream signalling pathways, such as: the JAK/ STAT signalling pathway, the MAPK signalling pathway and the PI3K pathway, which interact with each other and are involved in the formation of visceral hypersensitivity and intestinal inflammation in IBS. In addition, SCF increases the activation of intestinal MC induced by the receptor c-Kit, which causes MC to secrete 5-HT and so on, thus leading to intestinal motility disorders and visceral hypersensitivity[33].BDNF and TRPV1 are also closely related to 5-HT.TRPV1 regulates intestinal motility by mediating the release of 5-HT[34].The decrease of the expression of BDNF affects the synthesis of 5-HT[35], and the decrease of BDNF expression affects 5-HT synthesis[35], and BDNF also affects 5-HT synthesis[35]. At the same time, BDNF also agonises the MAPK and PI3K/AKT signaling pathways, which are involved in the development of IBS.

3. Discussion

In summary, Chinese medicine takes the holistic concept and evidence-based treatment as the starting point, and sums up the effective methods of treating IBS based on traditional compound prescriptions and modern prescription.The pathogenesis of IBS is the result of multifactors, and some scholars have proposed that IBS is caused by the irregular regulation of neuroimmunoendocrine network, and the traditional Chinese medicine compound prescriptions and acupuncture methods (e.g., the essential formula for pain and diarrhoea) can improve the symptoms of IBS by interfering with multiple signalling pathways, which coincides with the view that multiple mechanisms of IBS co-causes the disease.

The treatment of IBS with TCM has a broad application prospect, but there are still certain shortcomings: (1) the specific pathogenesis of IBS has not been fully elucidated at this stage, and the research on the intervention of TCM in the signalling pathway of IBS is relatively weak, and the role of various pathways in the pathogenesis of IBS and the interrelationships among various pathways still need to be further investigated; (2) in the replication of the model of IBS, there are fewer TCM evidence types, and the modelling methods used for different TCM evidence types are the same or similar, which may lead to confusion of the evidence; (3) in the study on the mechanism of TCM treatment of IBS, there is a great deal of potential for application. (2) During the replication process of IBS model, fewer Chinese medicine types are involved, and the modelling methods used for different Chinese medicine types are the same or similar, which may easily cause confusion of symptoms; (3) In the research on the mechanism of Chinese medicine in treating IBS, most of them focus on the study of a single protein of the signaling pathway, neglecting the study of other functional proteins affecting the signaling pathway; (4) Currently, Chinese medicine treatments are mostly for one person on one side, which has a strong targeting, and large-scale clinical applications need to be promoted by large samples. If a large-scale clinical application is to be promoted, a large sample of control studies is needed. In conclusion, there is still much room for the development of TCM in the treatment of IBS through the regulation of signalling pathways, and it is necessary to combine TCM with modern science and technology to continuously explore and provide strong objective evidence for the treatment of IBS with TCM.

References

[1] Ford A C, Lacy B E, Talley N J. Irritable Bowel Syndrome [J]. N Engl J Med, 2017, 376(26): 2566-2578.

[2] Ringel-Kulka T, Choi CH, Temas D, et al. Altered Colonic Bacterial Fermentation as a Potential Pathophysiological Factor in Irritable Bowel Syndrome [J]. Am J Gastroenterol, 2015, 110(9):1339-1346.

[3] Sinagra E, Morreale G C, Mohammadian G, et al. New therapeutic perspectives in irritable bowel syndrome: Targeting low-grade inflammation, immuno-neuroendocrine axis, motility, secretion and beyond [J]. World J Gastroenterol, 2017, 23 (36):6593-6627.

[4] Chu Haoran, Wang Yu, Tong Li, et al. Effects of moxibustion on TLR4/MyD88/NF-κB signalling pathway in the colon of rats with diarrhoeal irritable bowel syndrome [J]. Acupuncture Research, 2020, 45(08): 633-639.

[5] Zhao Ping, Yan Jing, Ji Lijiang. Efficacy of Qinghua antidiarrhoeal formula in treating diarrhoea-type irritable bowel syndrome with damp-heat in the spleen and stomach and its effect on serum inflammatory factors and TLR4/MyD88/NF-κB signalling pathway-related proteins [J]. Hebei

ISSN 2616-5791 Vol.4, Issue 8: 20-25, DOI: 10.25236/AJMHS.2023.040804

Traditional Chinese Medicine, 2021, 43(03): 375-379.
[6] Wu Jing, Du Xian, Yang Shasha, et al. Effects of Dajianzhong Tang on visceral pain in rats with irritable bowel syndrome [J]. Chinese Journal of Experimental Formulas, 2021, 27(06): 1-6.
[7] Zang X, Dou ZF. Progress on the correlation between brain gut peptide and irritable bowel syndrome [J]. Journal of Liaoning University of Traditional Chinese Medicine, 2019, 21(12): 110-115.
[8] Bouin M, Plourde V, Boivin M, et al. Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds[J]. Gastroenterology, 2002, 122(7): 1771-1777.
[9] Fang CF, Tang HM, Liao XH, et al. Effect of changji'an capsule on mRNA expressions of NPY and ACTH contents in brain-gut axis of IBS-D model rats [J]. Zhongguo Zhong Xi Yi Jie He Za Zhi, 2013, 33(7):948-952.
[10] Zhang Wei, Ge Wenjing, Wang Huisen, et al. Regulation of water metabolism and 5-HT system in rats with irritable bowel syndrome by Fangfeng, a meridian-inducing agent added and subtracted from Painful Diarrhoea Essentials Formula [J]. Chinese Journal of Experimental Formulas, 2020, 26(11): 56-62.
[11] Cai Linkun, Huang Shi, Peng Zhuoyu, et al. A study on the clinical efficacy of an intestinal soup for the treatment of diarrhoeal irritable bowel syndrome and its effect on serum 5-hydroxytryptamine levels from the perspective of visceral sensitivity [J]. Chinese Family Medicine, 2019, 22(36): 4488-4492+4498.
[12] Liang Ruifeng, Ge Wenjing, Wang Huisen, et al. Effects of Painful Diarrhoea Essentials Formula plus and minus meridian-inducing drug Fangfeng on visceral sensitivity and brain-gut peptides of different targets of brain-gut axis in rats with irritable bowel syndrome [J]. Chinese Journal of Experimental Formulas, 2018, 24(02): 152-157.
[13] Yang Mei, Li Yuxian, Liu Huan. Mechanism analysis of warm stomach and intestinal regulating granules intervening in diarrhoea-type irritable bowel syndrome based on brain-gut interaction axis [J]. Chinese Medicine Pharmacology and Clinic, 2019(6): 5.
[14] Aghazadeh Tabrizi M, Baraldi PG, Baraldi S, et al. Medicinal Chemistry, Pharmacology, and Clinical Implications of TRPV1 Receptor Antagonists[J]. Med Res Rev, 2017, 37(4): 936-983.
[15] Feng B, La JH, Schwartz ES, et al. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Neural and neuro-immune mechanisms of visceral hypersensitivity in irritable bowel syndrome [J]. Am J Physiol Gastrointest Liver Physiol, 2012, 302(10): G1085-G1098.
[16] Pisipati S, Connor B A, Riddle M S. Updates on the epidemiology, pathogenesis, diagnosis, and management of postinfectious irritable bowel syndrome [J]. Current Opinion in Infectious Diseases, 2020, 33(5): 411-418.
[17] Liu Lina, Yan Jing, Lu Weiting, et al. Effect of buckwheat extract in improving visceral nociceptive hypersensitivity in rats with irritable bowel syndrome and its mechanism[J]. West China Journal of Pharmacy, 2016, 31(02): 135-138.
[18] Han Yafei, Shi Lei, Jia Boyi, et al. Intervention effect of Painful Diarrhoea and An Intestine Formula on the expression of NGF/PLC-γ/TRPV1 signalling pathway in rats with diarrhoeal irritable bowel syndrome model [J]. China TCM Emergencies, 2017, 26(12): 2069-2073.
[19] Fang Jiansong, Ma Yuanping, Liu Chang, et al. PKA regulation of TRPV1 sensitisation mediates CGRP expression to explore the study of liver-sparing and spleen-strengthening formula for prevention and treatment of irritable bowel syndrome [J]. Chinese Journal of Traditional Chinese Medicine, 2017, 35(03): 601-604.
[20] Wu Haomeng, Tang Xudong, Wang Fengyun, et al. Mechanism of autophagy on the formation of visceral hypersensitivity in diarrhoeal irritable bowel syndrome [J]. Chinese Journal of Traditional Chinese Medicine, 2020, 35(12): 6261-6264.
[21] Huang Shi, Liu Peng, Lin Chunli, et al. Study on the expression of pPKCγ and ERK1 genes in dorsal root ganglia of rats with liver-depression and spleen-deficiency type irritable bowel syndrome[J]. Chinese Journal of Traditional Chinese Medicine, 2018, 36(01): 19-22.
[22] Guo Junxiong, Ma Li, Kang Wanrong, et al. Effects of Painful Diarrhoea Essentials Formula on the expression of p38 MAPK signalling pathway-related proteins and their target genes in colonic tissues of D-IBS rats with liver-depression and spleen-deficiency[J]. Chinese Journal of Experimental Formulas, 2020, 26(04): 1-8.
[23] Wang Shanshan, Wang Xurui, Yang Ruiyong, et al. Effectiveness of acupuncture combined with pain and diarrhoea formula in treating diarrhoea-type irritable bowel syndrome due to liver depression and spleen deficiency and its mechanism[J]. Chinese Acupuncture and Moxibustion, 2020, 40(06): 605-609.
[24] Wu Haomeng. Clinical and experimental study on the intervention of diarrhoeal irritable bowel syndrome by liver-sparing and spleen-strengthening method [D]. Guangzhou University of Traditional

ISSN 2616-5791 Vol.4, Issue 8: 20-25, DOI: 10.25236/AJMHS.2023.040804

Chinese Medicine, 2016.
[25] Xie Y, Zhan X, Tu J, et al. Atractylodes oil alleviates diarrhea-predominant irritable bowel syndrome by regulating intestinal inflammation and intestinal barrier via SCF/c-kit and MLCK/MLC2 pathways[J]. J Ethnopharmacol, 2021, 272:113925.
[26] Li Hui, Tian Yaozhou, Zhang Xunbing, et al. Effects of wind-extinguishing and dampness-resolving formula on visceral hypersensitivity in rats with diarrhoeal irritable bowel syndrome [J]. Journal of Nanjing University of Traditional Chinese Medicine, 2019, 35(06): 704-707.
[27] Rui Xiaowei, Zheng Sihui, Zhao Fangmin, et al. Effects of Painful Diarrhoea Essentials Formula on SCF/c-Kit signalling system in IBS-D rats with liver depression and spleen deficiency[J]. Zhejiang Journal of Traditional Chinese Medicine, 2021, 56(07): 472-474.
[28] Wan J, Ding Y, Tahir AH, er al. Electroacupuncture Attenuates Visceral Hypersensitivity by Inhibiting JAK2/STAT3 Signaling Pathway in the Descending Pain Modulation System [J]. Front Neurosci, 2017, 11:644.
[29] Lai Lei. Exploring the mechanism of Cultivation and Wood Suppression Method to alleviate IBS-D visceral hypersensitivity based on JAK-STAT signalling pathway [D]. Chengdu University of Traditional Chinese Medicine, 2018.
[30] Pan Xiaoou, Zhao Yan, Zhao Yuanqiao, et al. Effects of dendrobine on the expression of GFAP, NGF, BDNF and visceral sensitivity in mice with liver-depression and spleen-deficiency type irritable bowel syndrome [J]. Proprietary Chinese Medicine, 2021, 43(05): 1186-1190.
[31] Douglas, A, Drossman, et al. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction [J]. Gastroenterology, 2016, 150(6): 1257-1261.
[32] Xia Lixian, Zhou Jiaoli, Mei Lijun, et al. Mechanisms of diarrhoea-induced autophagy through PI3K-AKT pathway in the treatment of diarrhoeal irritable bowel syndrome [J]. World Journal of Integrative Medicine, 2021, 16(03): 468-471+504.
[33] Liang WJ, Zhang G, Luo HS, et al. Tryptase and Protease-Activated Receptor 2 Expression Levels in Irritable Bowel Syndrome [J]. Gut Liver, 2016, 10(3): 382-390.
[34] Wan Zhihua, Zhang Xin, Cai Yan. Changes of TRPV1, TRPA1 and 5-HT expression in rectal mucosa before and after surgery and quality of life analysis in patients with internal rectal prolapse [J]. Colorectal and Anal Surgery, 2017, 23(06): 756-759.
[35] Yang Yunsheng. Mechanisms of neuroimmunoendocrine network regulation in irritable bowel syndrome [J]. Journal of Gastroenterology and Hepatology, 2002, 11(4): 3.