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Progress in Signaling Pathways Associated to Irritable Bowel Syndrome

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Abstract: ***Irritable bowel syndrome (IBS) is the most common chronic functional bowel disease with abdominal pain and diarrhea as the main symptoms. Its course develops repeatedly, which seriously affects the quality of life of patients. At present, it occupies a large amount of medical resources, but its onset and etiology is not completely clear. It is currently believed that visceral hypersensitivity, brain-gut axis and gastrointestinal motility abnormalities are their important pathophysiology bases. In recent years, recent studies show that the signaling pathways in viscera and brain-gut axis, such as 5-HT, NF- κb, topv 1 and MAPK, have important effects on IBS. It can repair intestinal inflammation, reduce visceral sensitivity, enhance intestinal mucosal barrier and regulate intestinal power through the regulation of these series of signaling pathways, and plays an important role in multi-level, multi-link and multi-target treatment of IBS. Based on the signal pathway, this paper summarizes the research progress of IBS signal pathway in recent years, in order to provide theoretical support and diagnosis and treatment ideas for the clinical treatment of TCM in IBS.***

Keywords: Irritable bowel syndrome; Signaling pathway; Research progress**.**

1. Introduction

Irritable bowel syndrome (IBS) is a chronic non-organic gastrointestinal disease, which is characterized by changes in bowel habits and frequency, accompanied by varying degrees of abdominal pain and distension. According to the combination of stool characteristics and Bristol standard, the Rome III diagnostic guidelines classify IBS into 4 clinical subtypes, namely, diarrhea type (IBS-D), constipation tablet (IBS-C), mixed type (IBS-M) and undefined type (IBS-U), with IBS-D being the most common [1]. The incidence of IBS is 7%~16%, the pathogenesis is related to visceral hypersensitivity, intestinal hypersensitivity to normal contents, and the incidence of patients is often accompanied by a certain degree of psychological disorders, and the quality of life is seriously affected [2-4]. Although IBS is not a fatal disease, its course of disease is prolonged, and seriously affects the quality of life of patients. Western medicine believes that the pathophysiology of IBS is complex. At present, post inflammatory reaction, visceral hypersensitivity, intestinal mucosal barrier destruction, intestinal motility problems and brain-intestinal axis dysfunction are ordinary causes of IBS, but the exact mechanism is not completely clear [5], so it is extremely important to find the diagnosis and treatment targets of IBS. After searching a large number of literatures, it is found that the mechanism of action of traditional Chinese medicine in treating IBS is closely related to a variety of signaling pathways. This article reviews some signaling pathways to provide a comprehensive theoretical basis for clinical treatment of IBS.

2. 5-HT Signaling Pathway

5-HT, or 5-Hydroxytryptamine, also known as Serotonin, is an important biogenic amine neurotransmitter. It is widely distributed in the human body, especially in the cerebral cortex and synapses with high content, and is important substance the regulation of neural activities and mental emotions. The 5-h in the central nervous system accounts for about 5% of the total body, and the remaining 5-HT is found in the gastrointestinal tract. Enterochromaffin cells (EC cells) are the "production site" of 5-h in the gastrointestinal tract, and they produce about 90% of the total 5-h in the gastrointestinal tract. The central nervous system produces about 5% of the total 5-h in the human body, with the remaining 5-h present in the GI tract. Neurological studies have shown that 5-hydroxytryptamine (5-h), as a brain-intestinal peptide (BGP) with dual functions of neurotransmitter and hormone, affects visceral sensation, movement and secretion through brain-intestinal interaction (BGI), and is closely related [6-8] to the occurrence and development of IBS-D. When GBA regulatory function abnormalities lead to 5-h signaling pathway abnormal expression, affect 5-h synthesis, release, reuptake and other links, activate the downstream intestinal tissue receptors, cause gastrointestinal function and visceral sensitivity abnormalities. Enhanced hypersensitivity to physical and visceral stimulation, increases mucosal permeability, change intestinal peristalsis, activate the immune system to induce inflammation, thus showing IBS-D abdominal pain, diarrhea and other bedside symptoms, the mechanism is gradually considered to be an important pathophysiology basis of IBS-D.

Zheng Xue et al [11]. Took Zhongwan, Tianshu and Zusanli to treat IBS mice with natural moxibustion, and found that this method may be involved in regulating the brain-gut axis mediated by 5-HT pathway, thereby improving the visceral hypersensitivity state of mice. Zhu Xiaoqin et al [12]. Found that when 5-HT binds to 5-HT4 receptor, it can stimulate intestinal secretion of neurotransmitter and change intestinal motility, which can improve clinical symptoms related to defecation habits of IBS patients. When 5-h binds to 5-HT3 receptor, it can cause visceral hypersensitivity by transmitting damaging stimuli to the central nervous system. On this basis, Cao Jianan et al [13]. Also confirmed through animal

experiments that moxibustion can effectively reduce diarrhea symptoms and visceral hypersensitivity in IBS-D rats, which is related to inhibiting the expression of 5-HT and 5-HT3R in colonic tissue. Ouyang Yongwen et [14] al. Found that the expression level of 5-HT3R in rats in the transplantation group was significantly lower than that in the control group, while the expression level of 5-HT4R was significantly higher than that in the control group, with statistical significance ($P<0.01$), which also indirectly indicated that the influence on the binding of 5-HT to its receptor was also an important mechanism for the function of fecal bacteria transplantation. Zhang Jingxian et [15] al. Also found that Sini Powder had a synergistic effect on the rate-limiting enzyme of 5-h synthesis (i.e., TPH1) and related receptors (5-HT3R, 5-HT4R, etc.) In the colon of visceral hypersensitive rats. Another researcher Liang Guoqiang et [16] al. Found that Wumen Yicin had a bidirectional effect on 5-HT signal transduction in the colon and hypothalamus of IBS-D rats, and Wumen Yicin inhibited the expression of 5-HT4R in the colon. Sun Yanning [17] et al. Also observed the expression levels of TPH-1, 5-HT3R and SERT by using total glucoside of Paeony in modeling rats, and found that compared with the model group, the expression levels of TPH-1 and 5-HT3R in colonic tissues of rats in total glucoside of Paeony group were lower, and the expression levels of TPH-1 and 5-HT3R decreased with the increase of dose. Wei Xingxu et [18] al. Found that compared with the model group, the positive expression of 5-HT in the Sishen pill group and the Deishen pill group was decreased $p < 0.05$ or $p<0.01$, and the Sishen pill group was lower than the Deishen group ($p<0.05$) by using Sishen pill solution and Deishen pill solution respectively in rats. Compared the model group, the protein expression of 5-HT4R in Sishen Pill group and resistant group was increased ($p<0.05$ or $p<0.01$), and the expression of 5-HT4R in Sishen pill group was higher than that in resistant group ($p<0.05$). By observing the expression of colon clock gene Bmal1 in IBS model rats, Zeng et [19] al. Found that Bmal1 is seriously affected by circadian disturbance and may participate in the occurrence of IBS through colon EC cells and its TPH1**-**5**-**HT signaling pathway. This finding provides a new theoretical basis for explaining the mechanism of refractory IBS or completion rate disorder from the perspective of biological clock disorder.

In summary, the abnormal increase of 5-h in the gastrointestinal tract may lead to increased visceral sensitivity, and it is closely related to the regulation of mental emotions in the central system. In other words, the mental state may be observed to regulate the production of 5-HT. Therefore, 5-HT is an important link in the study of the brain-gut axis theory of IBS. The production, action and transport of IBS is related to EC cells, 5-h receptors (mainly 5-HT3R, 5-HT4R), Tryptophan hydroxylase (TPH) SERT-related. EC cells can spontaneously release 5-HT, and this process is enhanced when the gastrointestinal tract is stimulated. 5-h receptor is more complex, 5-h receptor is currently known to be divided into 7 families, 5-HT1-7R, a total of 14 sub [20] types, of which 5-HT3R and 5-HT4R is the most important, and are most closely related to the gastrointestinal tract. Animal experimental studies showed [21] that the expression of 5-HT3R in D-IBS model was significantly higher than that in blank control group. TPH, as an enzyme that triggers the production of 5-HT, plays an important role in its production. The regulation of 5-HT on gastrointestinal function not only requires the normal expression and secretion of 5-HT and its receptor, but also depends on the normal expression and function [22] of SERT.

The 5-h signaling system plays an extremely important physiological function in participating in and regulating gastrointestinal function. As an important signaling molecule, 5-HT is involved in gastrointestinal motility abnormalities and visceral hypersensitivity of IBS through its own regulation or interaction with a variety of receptors. Abnormalities in any link of the signal transduction system, such as synthesis, release, binding to corresponding receptors and reuptake of 5-HT, may lead to gastrointestinal motility abnormalities and visceral hypersensitivity. It can be seen that 5-h signaling system plays a crucial role in the pathogenesis of IBS.

3. NF-κB Signaling Pathway

Low-grade intestinal mucosal inflammatory response is one of the potential pathogenesis of IBS, and nuclear factor kappa B (NF-κB) is a key transcription factor in the inflammatory response. Nuclear factor Kappa (NF-kB) is a transcription factor associated with inflammatory response and can regulate a variety of inflammatory factors. In the resting state, the NF-kB subunit p50/p65 binds to the NF-kB suppressor protein (I kB) and exists in the cytoplasm in an inactive state [23]. Activation of NF-κB promotes Tumor Necrosis Factor α (TNF-α), interleukin (IL)-1β, and IL-8, which massively produces Necrosis Factor α (TNF-α) and leads to inflammatory response [24-25].

Zhu Wei et al. [26] compared the diarrhea IBS model rats with the blank group, the NF-kB level in the colon was significantly increased ($p<0.05$), while the NF protein expression level of F- κb in the treatment group decreased ($p <0.05$). Demonstrated that the intervention of NF-κb signaling was achieved to reduce the release of TNF- α, IL-6 and IL-1 β inflammatory factors, and thus to repair the damaged intestinal mucosa. He Xing [27] constructed the IBS-D rat model and found that the intestinal mucosa of IBS-D rats compared with normal rats highly expressed NF- κb (p65) protein and TLR 4 protein, the pro-inflammatory cytokine IL-8, MYD88 and TNF-α than normal rats, the inflammatory inhibitor IL-10 was lower than normal rats, however, after the use of the TLR 4/NF- κb signaling pathway blocker PDTC, could improve the associated symptoms in the IBS-D rats, further demonstrated that NF- κb signaling plays a critical role in the formation of IBS-D. Associated signaling pathways slow down intestinal inflammation and the oxidative stress response. Zhang Yujie et al [28] replicated the IBS model by avoiding water stress, and found that compared with the control group, the expression of protein kinase B (Akt) and NF-kB had decreased significantly ($p<0.05$), while the intestinal barrier protein [tight junction protein-1 (Claudin-1), closed protein (Occludin), and closed small protein-1 (ZO-1)] had increased. Wang Yu et al. [29] created the IBS-D rat model with chronic binding combined with diarrhea leaves. After 7d moxibustion interments, they found that the expression levels of IKK β, IKB α and NF-kB p65 protein in hippocampus and colon tissues were significantly reduced compared with the model group. Fu Rongpeng et al. [30]

observed the comparison of mrna expression levels of TLR 4 / MyD 88 / NF-κb signaling pathway in peripheral blood monocytes of 108 diarrheal IBS patients, and found no statistical difference between the two groups of TLR 4, MyD 88 and NF-κb mrna expression before treatment (P>0.05). TLR 4, MyD 88 and NF- κb mrna expression decreased after both treatment, and the study group was lower than the control group (p <0.05).

4. The TRPV1 Signaling Pathway

Topv 1 is a kind of non-selective cationic ligand gating channel, mainly expressed in medium and small nociceptive sensory neurons after activation, topv 1 conformation changes, open channel, the cation (mainly Ca^{2+}) permeability increase, trigger or activate a variety of important physiological activities, such as Neurotransmitter release, gland cell secretion and muscle contraction, etc. After the activation of TRPV 1 channel, there is a massive influx of extracellular calcium ions (Ca^{2+}), which increases the sensitivity of internal tissues and organs and mediates the production of pain sensitivity. IBS-D has a close relationship with TRPV 1 expression, and TRPV 1 expression enhancing [31] when abdominal pain. Deng Doxi et al [32]. Alleviated the visceral hypersensitivity of IBS rats by electroacupuncture and showed that electroacupuncture could reduce the expression of PAR 2, topv 1, SP, and CGRP proteins in the colon. He Yuxi et [33] al. Were molded and grouped. Compared with the normal group, the relative contents of TRPV 1, p-pk and p-CaMKII protein in the model group increased (p<0.05, p <0.01). Compared with the model group, topv 1 and p-pk decreased in the TCM group (p<0.05), and the relative content of topv 1 and p-pk decreased in the western medicine (p <0.05). However, [34] by Han Yafei et al detected colon NGF, PLC-γ and TRPV1 protein expression by Western Blot, real-time PCR was used to determine the expression of NGF, PLC-γ, TRPV1 mrna in the colon-colon, it was found that the expression of TRPV1 protein and TRPV1 mrna was significantly increased compared with the blank group, after the treatment, the two patients decreased significantly, the conclusion of the experiment showed that, can be detected by downregulation colonic NGF, PLC- γ, TRPV1 protein expression, reduce the colonic PLC- γ, TRPV1 mrna expression, Treatment with IBS-D.

5. MAPK Signaling Pathway

Mitogen-activated protein kinase (MAPK) signaling pathway is one of the important signal transduction systems in vivo, which is involved in many physiological and pathological processes such as cell-growth, development, division and differentiation. The signaling pathways of the MAPK family mainly include four pathways [35]: extracellular signaling regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK)/ stress-activated protein kinase (SAPK, P38MAPK and ERK5/BMK1). When cells are stimulated, mitogen-activated protein kinase kinase (MKK) and MKK kinase (MKKK) is phosphorylated step by step, regulating the transcription and expression of a series of downstream target genes. Abnormal activation of MAPK signaling pathway destroys local mucosal immune homeostasis in the intestine, mediating the occurrence and development [36] of IBS. Among them, P38MAPK signaling pathway is the most active, which is an important part of the MAPK family and is associated with inflammatory with the inflammatory response. After activation of p38 MAPK signaling pathway, the expression [37] of TNF-α, IL-1β, IL-6 and other downstream cytokines can be significantly increased. In order to verify the effect of Tongxieyao recipe on p38MAPK related signaling pathway in colonic tissue of IBS-D type with liver-stagnation and spleen-deficiency, Guo Junxiong et [37] al. Confirmed that the therapeutic effect of Tongxieyao recipe is related to inhibiting the expression of inflammatory factors in p38/MAPK signaling pathway through rat studies.

6. Nodules

In summary, 5-h signaling pathway, NF-κB signaling pathway, TRPV1 signaling pathway and MAPK signaling pathway are all pathways of action in the treatment of IBS, among which 5-HT signaling pathway and TRPV1 signaling pathway play an important role in mediating visceral hypersensitivity. The NF-κB signaling pathway and MAPK signaling pathway are closely related to mediating inflammatory response. Traditional Chinese medicine plays a huge role in the treatment of IBS. Through this series of signaling pathways, traditional Chinese medicine can reduce visceral sensitivity, slow down inflammatory response, enhance intestinal mucosal barrier and regulate intestinal motivity. Various experiments have proved that traditional Chinese medicine is involved in the treatment of IBS. There are many methods for the treatment of IBS-D in Chinese medicine. In general, there are many methods for the treatment of IBS-D in Chinese medicine, mainly mediated by two aspects. One is related pathway or target transduction through NF-κB and MAPK signaling pathways to reduce inflammatory response; the other is through mediating TRPV1, 5-h signaling pathway, down-regulating the expression of related pathways or proteins, increasing the gastrointestinal pain threshold, reducing visceral hypersensitivity [38]. Since the 1990s, the research on intracellular signal transduction pathway has gradually become a hot spot in the medical field at home and abroad. For IBS, more signaling pathways and their mechanisms need to be discovered and studied. The study of signaling pathway provides broad prospects for development for medicine research and disease treatment, and has important theoretical and practical significance.

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