Effects of Jianpi Huashi Granules on VIP and VIP R1 Receptors in the Colon of D-IBS Rats with Liver Depression and Spleen Deficiency Syndrome

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Abstract [**Objectives**] To investigate the effects of Jianpi Huashi Granules on colonic motility and the expression of vasoactive intestinal peptide (VIP) and its receptor 1 (VIP R1) in the colon of rats with diarrhea-predominant irritable bowel syndrome (D-IBS) of liver depression and spleen deficiency syndrome. [**Methods**] 90 SD rats were randomly divided into normal group, model group, positive drug group, Jianpi Huashi Granules low-/medium-/high-dose groups, as well as tonifying group, dampness-eliminating group, and liver-soothing group. The D-IBS model was established by intragastric administration of senna leaf decoction combined with restraint stress. The positive expressions of VIP and VIP R1 in the colon were detected by immunohistochemistry. Colonic motility curves were recorded using a four-channel physiological recorder, and the motility index was calculated. [**Results**] Compared with the normal group, the model group showed significantly increased colonic motility index and VIP expression ($P<0.01$), while no significant difference was observed in VIP R1 expression. Compared with the model group, all treatment groups exhibited significantly decreased motility index as well as VIP and VIP R1 expression ($P<0.05$, $P<0.01$). Compared with the high-dose group, the dampness-eliminating group showed a significantly increased motility index ($P<0.05$); the tonifying group and the liver-soothing group showed significantly increased VIP expression ($P<0.05$, $P<0.01$); and the liver-soothing group also showed significantly increased positive expression of VIP R1 ($P<0.05$). [**Conclusions**] Jianpi Huashi Granules can reduce the expression of VIP and VIP R1 in the colon of D-IBS rats and inhibit colonic motility, and the underlying mechanism may be related to the regulation of the brain-gut axis.

Key words Jianpi Huashi Granules, Liver depression and spleen deficiency syndrome, Vasoactive intestinal peptide, Colonic Motility index, D-IBS

1 Introduction

Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal pain and bloating, with symptoms related to defecation and/or accompanied by changes in bowel habits. It may present as diarrhea, constipation, or an alternation of both, along with abdominal distension, and the symptoms tend to recur and persist, with a relatively high prevalence among young and middle-aged populations[1]. According to the Rome IV criteria, IBS can be classified into four subtypes: diarrhea-predominant (D-IBS), constipation-predominant (C-IBS), unclassified (U-IBS), and mixed-type (M-IBS)[2]. Epidemiological studies have shown that the global prevalence of IBS is approximately 11.2%[3], with diarrhea-predominant IBS being the most common subtype. The pathogenesis of D-IBS remains incompletely understood to date. It is generally accepted that the development and aggravation of the disease involve a complex interplay of multiple factors, such as gastrointestinal infection, abnormal gastrointestinal motility, gastrointestinal hormones, intestinal inflammation and immune alterations, as well as neuropsychiatric and psychological factors[4]. In recent years, the brain-gut axis has attracted increasing attention. Brain-gut peptides, a class of small-molecule polypeptides that function as both neurotransmitters and gastrointestinal hormones, are considered crucial modulators of brain-gut axis activity[5]. Vasoactive intestinal peptide (VIP) is a brain-gut peptide derived from central and enteric neurons, and is abundantly distributed in both the central nervous system and peripheral tissues. It exerts vasodilatory and smooth muscle relaxant effects, and notably inhibits the contraction of gastrointestinal smooth muscle. Mechanistically, VIP retards gastrointestinal motility by enhancing the synthesis of nitric oxide and cyclic adenosine monophosphate, which in turn suppresses gastrointestinal contraction and diminishes gastric emptying and intestinal peristalsis[1]. With the progressive exploration of VIP and its receptors, the pleiotropic nature of VIP's biological functions has attracted considerable scientific interest. To better understand the therapeutic mechanism of Jianpi Huashi Granules in IBS, this study evaluated the expression profiles of VIP and its receptor 1 in the colonic tissue of D-IBS model rats.

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2 Materials and methods

2.1 Experimental animals Ninety SPF-grade male SD rats, with body weights of (200 ± 20) g, were obtained from Beijing

Huafukang Experimental Animal Technology Co., Ltd. (animal license No.: SCXK (Beijing) 2019-0008). The animals were acclimatized for one week under adaptive feeding conditions and subsequently housed in the barrier facility animal laboratory of Chengde Medical University. The study protocol was reviewed and approved by the Ethics Committee of Chengde Medical University (approval No.: CDMULAC-20210503-006). The 90 rats were then randomly assigned into 9 groups (10 rats in each group), namely the normal group, model group, positive drug group, Jianpi Huashi Granules low-, medium-, and high-dose groups, tonifying group, dampness-eliminating group, and liver-soothing group.

2.2 Drugs and reagents Senna Leaf (Beijing Bencao Fangyuan Pharmaceutical Group Co., Ltd., Batch No.: 20200409), identified as the dried leaflets of Cassia angustifolia, a leguminous plant. It was decocted twice with water and concentrated to a solution containing 0.6 g of crude drug per mL. The positive control drug was Pinaverium Bromide (ABBOTT LABORATORIES LIMITED, Batch No.: 713706), prepared as a 3 mg/mL solution with distilled water. Jianpi Huashi Granules were provided by the Institute of Chinese Materia Medica, Chengde Medical University. The granules were prepared from a proportional combination of ten Chinese medicinal materials: Astragali Radix Praeparata Cum Melle (Honey-Fried Huangqi), Alpiniae Oxyphyllae Fructus (Yizhiren), fried Atractylodis Macrocephalae Rhizoma (Stir-Fried Baizhu), Poria (Fuling), Amomi Fructus (Sharen), Linderae Radix (Wuyao), Citri Reticulatae Pericarpium (Chenpi), fried Paeoniae Radix Alba (Stir-Fried Baishao), Saposhnikoviae Radix (Fangfeng), and Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle (Honey-Fried Gancao). The preparation employed modern processes, including low-temperature dynamic water extraction, frozen concentration, spray drying, and dry granulation. The rabbit immunohistochemistry (SP) kit was obtained from Beijing Kangwei Century Biotechnology Co., Ltd. (Batch No.: 06623). The rabbit anti-rat primary antibodies for VIP and VIP R1 were purchased from BIOSS (Batch Nos.: BB04196976 and AI06128361, respectively).

Preparation of the decoction for the tonifying component group: Astragali Radix Praeparata Cum Melle, fried Atractylodis Macrocephalae Rhizoma, Alpiniae Oxyphyllae Fructus, and Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle from the Jianpi Huashi Formula were taken and proportionally combined according to the original formula ratio. The extract was prepared using the same process and was formulated into a solution containing 2.88 g of crude drug per mL immediately before use. Preparation of the decoction for the dampness-eliminating component group: Poria, Saposhnikoviae Radix, and Amomi Fructus from the Jianpi Huashi Formula were taken and proportionally combined according to the original formula ratio. The extract was prepared using the same process and was formulated into a solution containing 1.08 g of crude drug per mL immediately before use. Preparation of the decoction for the liver-soothing component group: Citri Reticulatae Pericarpium, fried Paeoniae Radix Alba, and Linderae Radix from the Jianpi Huashi Formula were taken and proportionally combined according to the original formula ratio. The extract was prepared using the same process and was formulated into a solution containing 1.08 g of crude drug per mL immediately before use. (Note: The concentrations of each component solution are equivalent to twice the clinically equivalent dose.)

2.3 Instruments The following instruments and equipment were used in this study: KD-TS3A automatic tissue dehydrator (Jinhua Kedi Instrument Equipment Co., Ltd., Zhejiang, China); KD-BMIII biological tissue freezing embedding machine, KD-2258 tissue microtome, and KD-P slide spreading machine (all from Jinhua Kedi Instrument Equipment Co., Ltd.); GZX-9240MBE electric blast drying oven (Shanghai Boyuan Industrial Co., Ltd.); BX53 microscopic medical imaging workstation (Olympus); Maclab/4e four-channel physiological recorder and QUAD Bridge biological amplifier (ADInstruments Pty Ltd., Australia); YP200 pressure transducer (Beijing Xinhang Xingye Technology and Trade Co., Ltd.); and a fluorescence upright microscope (Olympus Corporation, Japan).

2.4 Preparation of D-IBS rat model[6] Except for the normal group, rats in all other groups were administered senna leaf decoction by gavage daily for the first 2 weeks. From the 3rd week onward, after senna leaf administration, the rats were restrained with transparent tape around the forelimbs, chest, and shoulders for 2 h per day, lasting for 2 consecutive weeks. After successful modeling (*i.e.*, from the 5th week onward), each group was administered the corresponding drugs by gavage: the Jianpi Huashi Granules low-, medium-, and high-dose groups received solutions at concentrations of 0.625, 1.25, and 2.5 g/mL, respectively; the tonifying group, dampness-eliminating group, and liver-soothing group received the corresponding component decoctions (2.5 g/mL); the positive drug group received Pinaverium Bromide (3 mg/mL); the model group received normal saline by gavage daily and the normal group received only normal saline by gavage throughout the entire experiment. The gavage volume was 10 mL/kg for all groups. The medium dose of Jianpi Huashi Granules was equivalent to the clinically equivalent dose for adults. After the final administration, the rats were sacrificed, and colonic tissues were collected at 5 – 6 cm proximal to the anus. After rinsing with normal saline, one portion was stored at −80 ℃, and the other portion was fixed in 4% paraformaldehyde for immunohistochemical staining.

2.5 Determination of colonic motility index[7] The pressure transducer was connected to a four-channel physiological recorder. A syringe was filled with water and all air bubbles were expelled. The catheter (2 mm in diameter) of a self-made rubber balloon

was connected to a three-way stopcock (with one end connected to the pressure transducer and the other end to a 1 mL syringe), ensuring that the entire tubing system was airtight. Prior to the experiment, the rats were fasted for 16 h with free access to water. During the experiment, two drops of liquid paraffin were instilled into the anus of each rat to lubricate the intestinal tract. The rubber balloon and catheter, coated with liquid paraffin, were inserted 7 cm through the anus, and the catheter was secured to the base of the tail with medical tape. Water was slowly infused into the rubber balloon while the recording curves were monitored on the recorder. When the curve showed the most sensitive changes, the water infusion was stopped. After stabilization for 30 min, the recording was formally conducted for 30 min. The colonic motility curves of each group were observed, and the area under the curve within 5 min was calculated using the software supplied with the recorder as the colonic motility index.

2.6 Tissue collection and processing The rats in each group were sacrificed accordingly, and colonic tissues were collected. The colonic tissues from each group were divided into several small segments. From 3 rats in each group, one small segment of colon was fixed in 4% paraformaldehyde, followed by dehydration, paraffin embedding, sectioning, and then used for immunohistochemical staining.

2.7 Positive expression of vasoactive intestinal peptide (VIP) and VIP R1 Immunohistochemistry was employed for detection. Colon tissue sections were routinely dewaxed and hydrated, followed by antigen retrieval at 95 – 98 ℃ for 30 min and blocking with normal goat serum at 37 ℃ for 30 min. The sections were then incubated with primary antibodies (diluted at 1 ∶ 200, with PBS as negative control) overnight at 4 ℃, followed by incubation with secondary antibodies at 37 ℃ for 2 h. Diaminobenzidine (DAB) was used for chromogenic development, and the staining duration was controlled under a microscope. Positive reaction was defined as the presence of brownish-yellow precipitates in the cytoplasm, while the absence of such precipitates was considered negative. A deeper brownish-yellow color indicated a stronger positive reaction. Image J image analysis software was used for semi-quantitative analysis of target protein expression. For each section, six non-overlapping high-power fields were randomly selected, and the mean optical density was calculated after photography. The average value was taken as the expression level of the target protein in each rat.

2.8 Statistical analysis SPSS 27.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). For data that conformed to normal distribution and homogeneity of variance, one-way analysis of variance (ANOVA) was used for comparison among multiple groups, followed by *LSD* test when variances were equal, or Dunnett's T3 test when variances were unequal. For data not conforming to normal distribution, the rank-sum test was selected for intergroup comparison, and the Kruskal-Wallis H test was used for further pairwise comparisons. A P-value of <0.05 was considered statistically significant.

3 Results and analysis

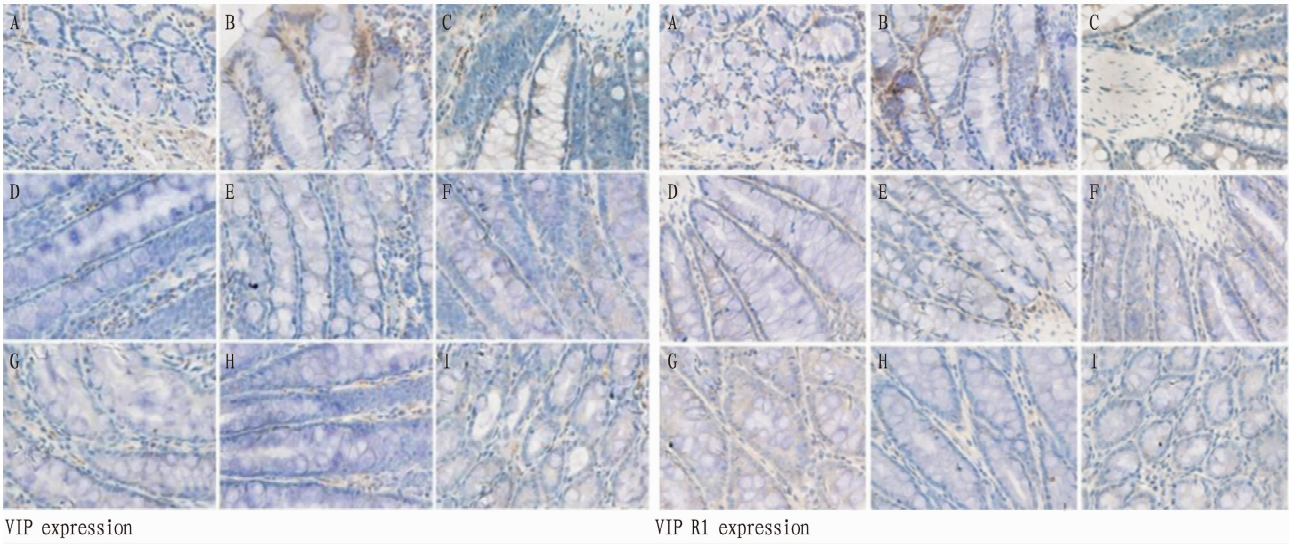
3.1 Change of mobility index Compared to the normal group, the model group exhibited a marked elevation in colonic motility index ($P < 0.01$). In contrast, when compared to the model group, the colonic motility index was significantly reduced in the positive drug group, the Jianpi Huashi Granules low- and high-dose groups, and the tonifying, dampness-eliminating, and liver-soothing groups ($P < 0.01$). Although the medium-dose group showed a lower value than the model group, this difference was not statistically significant ($P > 0.05$). In addition, the dampness-eliminating group displayed a significantly higher motility index compared to the high-dose group ($P < 0.05$). The results are presented in Table 1.

Table 1 Effects of senna leaf on colonic motility index in rats of each group ($\bar{x} \pm s$)

Group	Dose//g/kg	Motility index//mmHg/s
Normal	0.00	3 921.67 ± 472.01
Model	3.00	6 462.33 ± 405.27[2)]
Positive drug	0.03	3 556.89 ± 1 076.40[4)]
Low dose	6.25	2 633.22 ± 962.01[4)]
Medium dose	12.50	5 813.83 ± 215.61[6)]
High dose	25.00	2 571.78 ± 379.78[4)]
Tonifying	25.00	3 852.67 ± 1 623.09[4)]
Dampness-eliminating	25.00	4 170.56 ± 978.52[4)5)]
Liver-soothing	25.00	2 160.33 ± 248.66[4)]

NOTE Compared with the normal group: [1)] $P < 0.05$, [2)] $P < 0.01$; compared with the model group: [3)] $P < 0.05$, [4)] $P < 0.01$; compared with the high-dose group: [5)] $P < 0.05$, [6)] $P < 0.01$. The same as below.

3.2 Change of VIP and VIP R1 VIP positive expression was mainly localized in the glands and submucosa. Compared with the normal group, the positive expression of VIP in colonic tissue of the model group was significantly increased ($P < 0.01$), with deeper brownish-yellow staining; the positive expression of VIP R1 showed a numerical increase, but the difference was not statistically significant. Compared with the model group, the positive expressions of VIP and VIP R1 in colonic tissue were significantly decreased in the positive drug group and the Jianpi Huashi Granules low-, medium-, and high-dose groups ($P < 0.05$, $P < 0.01$). Compared with the high-dose group, the positive expression of VIP in colonic tissue was significantly increased in the tonifying group and the liver-soothing group ($P < 0.05$, $P < 0.05$), and the positive expression of VIP R1 in colonic tissue was also significantly increased in the liver-soothing group ($P < 0.05$). The dampness-eliminating group also showed an increase, but the difference was not statistically significant ($P > 0.05$), as shown Fig. 1 and Table 2.



NOTE A. Normal, B. Model, C. Positive drug, D. Low dose, E. Medium dose, F. High dose, G. Tonifying, H. Dampness-eliminating, I. Liver-soothing.

Fig. 1 Effects of each group on the expression of VIP and VIP R1 in the colonic mucosa of rats

Table 2 Mean optical density values of VIP and VIP R1 in colonic tissues of rats in each group ($\bar{x} \pm s$, $n = 6$)

Group	Dose	VIP	VIP R1
Normal	0.00	0.098 8 ± 0.010 5	0.123 5 ± 0.006 8
Model	3.00	0.147 2 ± 0.005 7$^{2)}$	0.136 0 ± 0.004 6
Positive drug	0.03	0.103 5 ± 0.003 8$^{4)}$	0.125 5 ± 0.002 2$^{3)}$
Low dose	6.25	0.107 7 ± 0.004 0$^{4)}$	0.117 0 ± 0.001 4$^{4)}$
Medium dose	12.50	0.106 0 ± 0.001 4$^{4)}$	0.107 5 ± 0.002 0$^{4)}$
High dose	25.00	0.104 2 ± 0.002 3$^{4)}$	0.097 8 ± 0.009 8$^{4)}$
Tonifying	25.00	0.111 7 ± 0.004 3$^{4)5)}$	0.101 8 ± 0.002 5$^{4)}$
Dampness-eliminating	25.00	0.116 7 ± 0.007 0$^{4)}$	0.101 2 ± 0.002 8$^{4)}$
Liver-soothing	25.00	0.117 3 ± 0.001 4$^{4)6)}$	0.122 0 ± 0.004 7$^{4)5)}$

4 Discussion

Diarrhea-predominant irritable bowel syndrome (D-IBS) is a common functional gastrointestinal disorder, and its pathogenesis has not been fully elucidated[8]. In traditional Chinese medicine, D-IBS is classified under the categories of "abdominal pain" and "diarrhea"[9]. Studies have confirmed that the pathogenesis of IBS is closely related to factors such as brain-gut axis dysfunction, abnormal secretion of brain-gut peptides, mast cell activation, and altered expression of aquaporins, which may be the major factors leading to the development of D-IBS. Among these, brain-gut axis abnormalities are closely associated with changes in brain-gut peptide levels; abnormal brain-gut peptides can induce mast cell degranulation and trigger inflammatory responses, which in turn affect aquaporin levels and lead to diarrhea[10]. VIP, an important inhibitory neurotransmitter in the enteric nervous system, is also a representative neuropeptide that participates in the information transmission and regulation of various physiological functions as a signaling molecule. It is distributed in the liver, biliary tract, pancreas, gastrointestinal tract, and other tissues, and is closely related to digestive system diseases. Once its content and receptor sensitivity undergo changes, it can cause multi-system diseases, particularly leading to secretory dysfunction of the digestive system[11]. VIP-R1 is a subtype of the VIP family and belongs to the G protein-coupled receptors. Upon binding to VIP R1, VIP activates the coupled Gs subunit of the G protein, which stimulates adenylate cyclase (AC) to generate cAMP via transmembrane signal transduction. cAMP subsequently activates cAMP-dependent protein kinase A (PKA), which catalyzes the phosphorylation of serine residues on aquaporins, activating colonic mucosal aquaporins (AQPs). This in turn increases membrane permeability, leading to substantial water transport into the intestinal lumen and resulting in diarrhea[12].

Current research on traditional Chinese medicine treatment for D-IBS has predominantly centered on the therapeutic efficacy and underlying mechanisms of herbal prescriptions. However, the IBS models commonly employed in these studies can only replicate a portion of the symptomatology, and thus fail to fully recapitulate the complex pathogenesis and clinical manifestations of human D-IBS, resulting in certain discrepancies from the actual clinical pathophysiological processes. Our previous investigations revealed that during model induction, the colonic motility index as well as the expression of AQP3 and AQP4 in rats undergo marked alterations under varying pathological conditions[7, 13]. The present study revealed that rats with D-IBS of liver depression and spleen deficiency syndrome exhibited significantly increased colonic VIP and VIP R1 expression as well as an elevated colonic motility index, suggesting that activation of the VIP signaling pathway may contribute to diarrhea development by enhancing membrane permeability. Following treatment with Pinaverium Bromide or Jianpi Huashi Granules at different dosages, both the colonic motility index and the levels of VIP and VIP R1 were markedly decreased

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relative to the model group. These findings suggest that Jianpi Huashi Granules may exert its therapeutic effects by modulating VIP and VIP R1 expression, thereby regulating aquaporin activity, reducing membrane permeability, and attenuating gastrointestinal motility, which in turn alleviates D-IBS-associated abdominal pain and intestinal dysfunction. On this basis, we hypothesize that the involvement of spleen deficiency and liver depression syndrome in D-IBS pathogenesis may be attributable to brain-gut axis dysregulation, with the underlying material basis reflected in altered levels of brain-gut peptides including VIP and VIP R1.

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