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Pingwei capsules improve gastrointestinal motility in rats with functional dyspepsia

Liang Qiankun[a], Mao Lanfang[b], Du Xiaojuan[b], Li Yunxia[a], Yan Yuan[a], Liang Jingjing[a], Liu Junhong[b], Wang Longde[b], Li Hongfang[a,c,*]

[a] Department of Physiology, College of Basic Medicine, Lanzhou University, Lanzhou 730000, China
[b] Department of Gastroenterology, Affiliated Hospital, Gansu Chinese Medical College, Lanzhou 730020, China
[c] Key Laboratory of Preclinical Study for New Drugs of Gansu Province, Lanzhou 730000, China

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ABSTRACT

Objective: To investigate the mechanism of Pingwei capsules (PWC) in improving gastrointestinal motility in rats with functional dyspepsia (FD).
Methods: We established an FD model by stimulating semi-starvation rats *via* tail damping, provocation, and forced exercise fatigue. The FD model group was further divided into five groups according to the treatment received: normal saline, domperidone, low-dose PWC, mid-dose PWC, or high-dose PWC. The effect of PWC on FD was evaluated by measuring gastrointestinal motility. Changes in leptin and cholecystokinin (CCK) were detected through enzyme-linked immunosorbent assay, reverse transcription-polymerase chain reaction, and immunohistochemistry.
Results: PWC significantly increased gastrointestinal motility in FD rats. Furthermore, PWC significantly increased CCK mRNA and protein concentrations in the duodenum and antrum, decreased leptin protein concentrations in the duodenum, antrum, and hypothalamus, and decreased CCK protein concentration in the hypothalamus.
Conclusion: PWC improves gastrointestinal motor function in FD rats by decreasing the leptin concentration in serum and the brain-gut axis, and by increasing the CCK concentration in gastrointestinal tissue. Our findings help to elucidate the mechanism of FD and provide further insight into the pharmacokinetics of PWC.

1. Introduction

Functional dyspepsia (FD) is a common clinical gastrointestinal disorder that is characterized by persistent or recurrent pain and discomfort in the absence of any organic disease. FD has a negative impact on the quality of life and health of patients [1], despite causing minimal or no mortality. Although many FD studies have been performed [2–5], the mechanism of FD remains unclear. Determining the mechanism of FD is particularly challenging because there are several types of FD, including dysmotility, non-ulcer and reflux dyspepsia [6,7], and each FD type has varying clinical symptoms. Previous studies have reported the main clinical symptoms of FD as antral hypomotility [8–10] and delayed gastric emptying [11], which is clinically characterized by a feeling of fullness, upper abdominal discomfort, early satiety, or nausea [12].

Bidirectional brain-gut interactions play an important role in the regulation of physiological activities in gastrointestinal tract disease. For example, dysregulation of the central nervous system (CNS) and enteric nervous system (ENS) in FD leads to alterations in sensation, motility, mood, and affect [13]. Information from the local sensory inputs of the gastrointestinal tract is transmitted to the CNS *via* various visceral afferent pathways (enteric, spinal, and vagal) [14]. These communication pathways between the ENS and CNS may involve brain-gut peptides [15].

Circulating leptin penetrates the blood-brain barrier *via* a receptor-mediated transport system [16,17], and acts on the leptin receptor in the medial hypothalamus to affect the regulation of energy balance and feeding behavior [18]. In contrast, the blood-brain barrier cannot be crossed by cholecystokinin (CCK), which is secreted in the gastrointestinal tract in connection with gastrointestinal motility [19]. The CCK signal reaches the hypothalamus via

* Corresponding author at: Department of Physiology, College of Basic Medicine, Lanzhou University, Lanzhou 730000, China.
E-mail address: lihf@lzu.edu.cn (L. Hongfang).

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Table 1
Components of Pingwei capsules.

Herb	Therapeutic effect	Proportion (100%)
Cangzhu (*Rhizoma Atractylodis Lanceae*)	Improvement of gastrointestinal motility [30–33]	6.8
Houpu (*Cortex Magnoliae Officinalis*)	Anti-inflammatory and anti-depression [34–36]	6.8
Muxiang (*Radix Aucklandiae*)	Spasmolytic role in gastrointestinal motility [37]	5.6
Zhiqiao (*Fructus Aurantii Submaturus*)	Anti-tumor [38,39]	6.8
Chenpi (*Pericarpium Citri Reticulatae*)	Anti-inflammatory and weight increase [40,41]	5.6
Chaihu (*Radix Bupleuri Chinensis*)	Anti-depression [42]	6.8
Baishao (*Radix Paeoniae Alba*)	Anti-inflammatory and anti-depression [43–46]	5.6
Baiji (*Rhizoma Bletillae Striatae*)	Anti-inflammatory and anti-aging [47,48]	6.8
Sanleng (*Rhizoma Sparganii*)	Anti-tumor and the abdomen pain remission [49,50]	5.6
Haipiaoxiao (*Endoconcha Sepiellae*)	Anti-inflammatory and gastroprotective potential [51,52]	6.8
Jineijin (*Endothelium Coreneum Gigeriae Galli*)	Promotion of digestion and circulation [50,53]	8.5
Zhebeimu (*Bulbus Fritillariae Thunbergii*)	Anti-inflammatory [54]	5.6
Huanglian (*Rhizoma Coptidis*)	Anti-inflammatory [55]	3
Pugongying (*Herba Taraxaci Mongolici*)	Anti-inflammatory and analgesic activity [56]	8.5
Yanhusuo (*Rhizoma Corydalis Yanhusuo*)	Anxiolysis [57]	5.6
Ezhu (*Rhizoma Curcumae Phaeocaulis*)	Anti-inflammatory and anti-tumor [58,59]	5.6

the vagal reflex pathway, which is involved in feedback suppression of gastrointestinal motility [20].

In clinical practice, gastrointestinal motility can be increased by prescribing cisapride, itopride, and metoclopramide; however, these drugs are no longer used for this purpose due to associated adverse effects [21]. The gastroprokinetic drug domperidone is used in many countries, but is not available in the USA without a prescription, as it has not been approved by the US Food and Drug Administration [22]. Thus, there is a need for safe and effective prokinetic agents that increase gastrointestinal motility.

Pingwei capsules (PWC) were developed from the traditional Chinese medicine Pingwei San (PWS; Pyungwi-San in Korea). PWS is a classic drug used during the Song Dynasty in China; it plays a key role in the treatment of gastritis, esophageal reflux, gastric or duodenal ulcers, and acute or chronic enteritis [23–26]. The PWS formula was first published in the *Prescriptions of Taiping Benevolent Dispensary* [27], and consists of six herbs: Cangzhu (*Rhizoma Atractylodis Lanceae*), Houpu (*Cortex Magnoliae Officinalis*), Chenpi (*Pericarpium Citri Reticulatae*), Gancao (*Radix Glycyrrhizae*), Shengjiang (*Rhizoma Zingiberis Recens*), and Dazao (*Fructus Jujubae*). In the USA, PWS could potentially be used as a substitute for cisapride in the treatment of heartburn and gastritis [28]. The most effective herbal composition and dosage of PWC was developed at the Affiliated Hospital of Gansu Chinese Medical College according to modern medicine pathogenesis, pharmacological research, and clinical experience. PWC comprises 16 herbs that possess clear therapeutic effects (Table 1); clinicians at the Affiliated Hospital of Gansu Chinese Medical College have used PWC to treat FD for many years. A paper published by the Affiliated Hospital of Gansu Chinese Medical College reported that PWC can significantly improve upper abdominal fullness, early satiety, belching, heartburn, nausea, vomiting, and other symptoms in patients with FD [29], but the mechanism by which PWC improves FD in rats remains unclear.

The purpose of the present study was to explore the mechanism by which PWC improves gastrointestinal motility in terms of brain-gut peptides and the brain-gut axis. We used a tail damping FD rat model that simulates the development of FD in humans; this rat model displays several key features of human FD, such as reduced food intake, bodyweight reduction, irritability, aggression, and gastrointestinal hypomotility [60–62].

2. Materials and methods

2.1. Animal model

All animal procedures carried out in the present study were reviewed, approved, and supervised by the Institutional Animal Care and Use Committee of the Ethics Committee of Lanzhou University, China (certificate of quality No. SCXK [gan] 2013–0002).

Thirty-six healthy male Wistar rats (clean grade, 7-weeks-old, weighing 180–220 g) were obtained from the Experimental Animal Center of Lanzhou University. PWC were supplied by the Affiliated Hospital of Gansu Chinese Medical College (drug approval number: Z120022224). The rats were housed in a restricted-access laboratory with a controlled temperature of 25 °C and a light: dark cycle of 12 h:12 h. Two pairs of bipolar stainless steel electrodes were implanted 3 mm apart onto the serosal surface of the gastrointestinal tract in each rat. One pair was implanted on the antrum (1 cm distal to the pylorus), and the other was implanted on the small intestine (1–2 cm distal to the pylorus). The free ends of the electrodes were brought subcutaneously to the back of the neck. After 1 week of conventional feeding, the rats were randomized into a control group ($n=8$) and an FD model group ($n=28$) using a random number table method. The number of laboratory rats necessary was calculated according to previously reported animal experiments [63].

The FD model was established by stimulating semi-starvation rats via tail damping, provocation, and forced exercise fatigue [60–62], this stimulation was performed four times a day for 10 d. In detail, we used a long sponge-holding forceps and clamped the distal 1/3 of the tail, without causing damage to the skin. The tail clamping was performed for 30 min each time, after which the rats ran on an experimental treadmill at an appropriate speed for 10 min to induce forced exercise fatigue. These experimental procedures were performed at 9:00, 12:00, 15:00, and 18:00 for 10 consecutive days, with alternate day feeding. Bodyweight and food intake were recorded. If the skin on the tail ruptured, iodophor was applied to the wound. The random number table method was used to randomly divide the 28 model rats into five groups: a model group ($n=8$, received 4 mL of normal saline daily), a domperidone-treated group (domp group, $n=5$, 10 mg kg^{-1} d^{-1}), a low-dose PWC-treated group (PWC I group, $n=5$, 1.6 g kg^{-1} d^{-1}), a middle dose PWC-treated group (PWC II group, $n=5$, 3.2 g kg^{-1} d^{-1}), and a high dose PWC-treated group (PWC III group, $n=5$, 4.8 g kg^{-1} d^{-1}). The control group received 4 mL of normal saline daily. The rats received 4 mL of drug or normal saline daily by oral gavage for 21 d using straight gavage needles 1 (Globalebio, Beijing, China) for 150–300 g bodyweight (16 gauge, 3-inch length, 3-mm ball diameter). Then, the gastrointestinal electrical activity was recorded by a microcomputer with a BL-420S experimental system biological function analyzer (TaiMeng Technology, Chengdu, China). The frequency and amplitude of slow wave and spike activity in the duodenum and antrum were recorded for 1 h.

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