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ORIGINAL ARTICLE

Decreased glucagon-like peptide-1 correlates with abdominal pain in patients with constipation-predominant irritable bowel syndrome

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Summary
Background and objective: The glucagon-like peptide-1 (GLP-1) analog, ROSE-010, plays a critical role in alleviating abdominal pain in patients with irritable bowel syndrome (IBS); however, the underling mechanism is unclear. In the present study, we determined the serum GLP-1 level in patients with constipation-predominant IBS (IBS-C). The relationship between GLP-1 and abdominal pain was investigated. In addition, the expression of the GLP-1 receptor in the colon was determined.
Methods: Rectosigmoid biopsies were gathered from 38 patients with IBS-C who met the Rome III criteria, and 22 healthy controls. Abdominal pain was quantified by a validated questionnaire. Serum GLP-1 was measured by ELISA and correlated with abdominal pain scores. The presence of the GLP-1 receptor in the colonic mucosa was assessed by immunohistochemistry.
Results: Serum GLP-1 was substantially decreased in patients with IBS-C. Decreased serum GLP-1 had a negative correlation with the abdominal pain scores. Biopsies from patients with IBS-C revealed a significant down-regulation of the GLP-1 receptor in colonic mucosa compared with control subjects.
Conclusions: Decreased serum GLP-1 correlates with abdominal pain in patients with IBS-C. Decreased expression of GLP-1 and GLP-1 receptor may be the basis for alleviation of abdominal pain in patients with IBS-C by ROSE-010.

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Introduction

Irritable bowel syndrome (IBS) is a functional intestinal disorder characterized by abdominal pain and discomfort associated with altered bowel habits [1]. IBS affects nearly 15% of the world's population, and has a female predominance [2–4]. Although IBS does not affect life expectancy, IBS seriously reduces the quality of life. According to ROME III criteria and predominant bowel symptoms, IBS is classed into four subgroups, as follows: IBS-constipation (IBS-C); IBS-diarrhea (IBS-D); IBS-mixed and unsubtyped IBS. The symptom-based ROME III diagnostic standard for IBS-C include hard or lumpy stools $\geq$ 25% of the time and loose or watery stools < 25% of the time [5].

Abdominal pain and discomfort is the main complaint, which leads to patient's medical consultation and is believed to be the clinical hallmark of IBS [6]. Although the pathogenesis of IBS-associated abdominal pain/discomfort is poorly understood, there is general agreement that the increased sensitivity to stimuli from the intestinal wall (i.e., visceral hypersensitivity) is a contributing factor. It is believed that several mechanisms are involved in the visceral hypersensitivity in IBS patients [7], including:

- the increased perception of the intestinal signal in the central nervous system;
- hypersensitivity of dorsal horn neurons in the central limb of the visceral afferent pathway;
- hyperexcitability of sensory neural endings at the end-organ level.

The causes underlying end-organ hypersensitivity in IBS have been increasingly investigated.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells located predominantly in the ileum and colon. GLP-1 is considered to enhance glucose-stimulated insulin secretion and reduce gastric emptying and small bowel motility [8]. GLP-1 exerts biological effects by binding to its specific receptor (GLP-1 R), which is expressed in the stomach, pancreas, intestines, and brain [9].

In humans, GLP-1 decreases small intestinal motility in healthy subjects and patients with IBS [8]. A prior case report indicated marked prolongation of large intestinal transit in a patient with a neuroendocrine tumor that secreted GLP-1 and GLP-2 [10]. In a study of 118 patients with functional constipation or IBS-C, delayed colonic transit was detected in IBS-C patients more frequently [11]. It is seemed that GLP-1 is associated with delayed colonic transmit.

However, it was reported a synthetic GLP-1 analog ROSE-010 increases colonic transit in another study [12]. ROSE-010 also reduced abdominal pain in IBS patients [13]. And the underling mechanism is still unknown. So, we elected to study patients with IBS-C because of the need to demonstrate the relationship between GLP-1 level and abdominal pain in IBS-C patients.

In the present study, we investigated serum GLP-1 and GLP-1 receptor in colonic mucosa in IBS-C patients and control subjects. The correlation between abdominal pain scores and GLP-1 was determined in all participants. The data obtained will provide a new theoretical basis for ROSE-010 treatment in IBS-C patients.

Materials and methods

Subjects

The data were collected between August 2012 and April 2015 in the Gastroenterology Department of Dalian Friendship Hospital. Thirty-eight patients with IBS-C (21 females and 17 males; mean age, 48.5 $\pm$ 9.5 years) and 22 control subjects (13 females and 9 males; mean age, 48.1 $\pm$ 9.8 years) participated in the research. This research was approved by the Ethical Review Board of Dalian Friendship Hospital, and all participants provided written informed consent before participating in this study. The diagnosis of IBS-C was made based on the ROME III criteria and exclusion of organic disease. The patients satisfying the following criteria were included [14]:

- in the last 3 months, the patient had abdominal pain or discomfort for $\geq$ 3 days every month. The duration of pain or discomfort was $\geq$ 6 months;
- in the last 3 months, loose or watery stools occurred < 25% of the time and hard or lumpy stools occurred $\geq$ 25% of the time;
- the following items were related to ''discomfort/pain'' some of the time:
  - improved by a bowel movement,
  - association with an alteration in the frequency of bowel movements, such as having more or fewer bowel movements;
- any of the above symptoms had taken place recently $\geq$ 2 days every week.

None of the participants were receiving non-steroidal anti-inflammatory drugs, other anti-inflammatory drugs (including mast cell stabilizers, probiotics, immunosuppressants, and steroids), or pain medications. Further, none of the participants had undergone major abdominal surgery, had any organic diseases, asthma, celiac disease, colon cancer, other tumors, or gastrointestinal diseases. Female participants with associated symptoms, such as irritable bladder, dysmenorrhea, chronic pelvic pain syndrome, and other painful gynecologic disorders were also excluded. Control subjects were chosen from patients undergoing colonoscopy for polyps or cancer surveillance, and all of the participants had negative results.

All participants underwent colonoscopy after a standard bowel preparation with polyethylene glycol electrolyte powder, and a saline enema was used for cleansing stool if necessary. All colon samples were obtained from the rectosigmoid junction for the standardization of the sample site. In all cases, two mucosal biopsy specimens were obtained for routine haematoxylin and eosin (H&E) staining histology and immunohistochemistry. Blood samples were collected for enzyme linked immunosorbent assay (ELISA) essay in all participants at 07:00 before intake of breakfast or water.

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