Rome III Functional Constipation and Irritable Bowel Syndrome With Constipation Are Similar Disorders Within a Spectrum of Sensitization, Regulated by Serotonin

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of these questions, successful learners will be able to discuss the symptoms and pathophysiology of irritable bowel syndrome with constipation and functional constipation.

BACKGROUND & AIMS: Patients with irritable bowel syndrome with constipation (IBS-C) and patients with functional constipation (FC) have similar symptoms, and these disorders overlap in their diagnostic features. Little is known about their overlap in physiology or the involvement of serotonin signaling. We investigated relationships between platelet-depleted plasma concentrations of serotonin, gastrointestinal symptoms, and motor–sensory function in patients with FC or IBS-C compared with healthy volunteers (controls). **METHODS:** We measured platelet-depleted plasma concentrations of serotonin in fasting and fed individuals with IBS-C (n = 23; 19–50 years old), FC (n = 11; 25–46 years old), and controls (n = 23; 20–49 years old) recruited in Manchester, UK. We also quantified abdominal and bowel-related symptoms, rectal sensitivity, oro-cecal transit, and colonic (whole intestine) transit. **RESULTS:** Patients with IBS-C or FC had similar baseline symptoms, bowel habits, oro-cecal and colonic transit, and fasting concentrations of serotonin and response to meal ingestion. Only patients with IBS-C had increased symptoms after ingestion of a meal ($P < .001$)—these patients tended to have lower sensory thresholds than patients with FC. Defecation frequency in the combined group of patients with IBS-C or FC correlated inversely with serotonin concentration ($r = -0.4$; $P = .03$). Serotonin concentration also correlated with pain threshold ($r = 0.4$; $P = .02$) and stool threshold ($r = 0.5$; $P = .06$), which correlated inversely with defecation frequency ($r = -0.3$; $P = .10$). **CONCLUSIONS: FC and IBS-C, based on Rome III criteria, are not distinct disorders, symptomatically or physiologically. Instead, they appear to lie in a spectrum of visceral sensitivity modulated by serotonin signaling. Symptom response to meal ingestion should be considered in patient classification.**

Keywords: Visceral Sensitivity; 5-Hydroxytryptamine; 5-HT; Neurotransmitter.

The Rome III criteria for functional gastrointestinal disorders separates irritable bowel syndrome with constipation (IBS-C) and functional constipation (FC) into separate entities and excludes a diagnosis of FC in patients satisfying the criteria for IBS-C.[1] Recent studies, however, suggest that there is a lack of symptom profile specificity and much diagnostic overlap between these 2 groups, and that they might be part of the same condition, with patients located along a spectrum of pain/discomfort severity.[2] In addition to the symptoms associated with defecation overlapping, such as straining, hard/lumpy stools, sense of incomplete evacuation, difficulty passing stool, and bloating,[3] recent studies have shown that 44% of FC patients report abdominal pain/discomfort, symptoms included in the Rome diagnostic criteria for IBS but not for FC.[2] During a 12-month period, approximately one third of patients switched diagnosis.[2] Studies have also shown that pathophysiology is often similar, with both groups exhibiting reduced numbers of high-amplitude propagated colonic contractions,[4] delayed transit, and alterations in visceral sensitivity,[1] although more FC patients exhibit hyposensitivity than IBS-C patients.[5]

5-hydroxytryptamine (5-HT) is a biogenic amine synthesized primarily in the gastrointestinal tract and stored in the mucosal enterochromaffin (EC) cells.[6] Once released in response to mechanical and chemical stimulation, it activates receptors on intrinsic and extrinsic nerves to regulate peristalsis, enhance secretion, and modulate sensory transmission between the gut and central nervous system. Studies in IBS-C and FC patients have shown elevated levels of 5-HT in the mucosa of the gastrointestinal tract.[7–10] In addition, IBS-C patients have been shown to exhibit lower concentrations of platelet-depleted plasma (PDP) 5-HT after meal ingestion

Abbreviations used in this paper: EC, enterochromaffin; FC, functional constipation; 5-HT, 5-hydroxytryptamine; HV, healthy volunteer; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; PDP, platelet-depleted plasma; SSRI, selective serotonin reuptake inhibitor.

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than healthy volunteers (HVs), concentrations remaining very similar to fasting conditions.[11] This observation, along with those showing similarly low levels of PDP 5-hydroxyindoleacetic acid, a metabolite of 5-HT, but similar 5-hydroxyindoleacetic acid to 5-HT ratio to HVs,[11] suggests a problem with release of 5-HT to physiological stimuli in IBS-C patients. No similar studies have been performed in FC patients.

Studies relating physiological changes in the 5-HT system to motor-sensory function are limited. One study combining patients with IBS-C and IBS with diarrhea (IBS-D) showed a direct correlation between PDP 5-HT concentration and colonic motility,[12] while another combining IBS-C and postinfectious IBS patients reported a weak negative correlation between PDP 5-HT and colonic transit time.[13] No data were reported for bowel habit subtypes separately, and no studies have examined the relationship between physiological concentrations of PDP 5-HT and visceral sensitivity. However, acutely decreasing serotonergic activity by tryptophan depletion, which decreases plasma 5-HT, has been shown to increase visceral sensitivity in IBS-D patients,[14] and acutely increasing serotonergic activity with the selective serotonin reuptake inhibitor (SSRI), citalopram, has been shown to have no effect,[15] with neither tryptophan depletion nor SSRIs having any effect on rectal motor function.[16] Likewise, 6 weeks treatment with fluoxetine, another SSRI, had no effect on visceral sensitivity in a nondepressed mixed group of IBS patients with diarrhea, constipation, or alternating bowel habit.[17]

The aim of this study was to compare fasting and fed PDP 5-HT concentrations and 5-HT response to meal ingestion in FC patients, with IBS-C patients and HVs, and to examine the relationships to symptoms and motor–sensory function. In addition, these physiological data were used to provide additional evidence as to whether FC and IBS-C defined by Rome III are distinct conditions.

Materials and Methods

Subjects

This study was carried out on 24 female IBS-C patients (aged 19–50 years), 12 female FC patients (aged 25–46 years), and 24 female HVs (aged 20–49 years). Patients were recruited from the Outpatients Department of the University Hospitals of South Manchester (tertiary patients excluded), local general practices, advertisement in regional newspapers, and an existing departmental volunteer pool of patients, and all satisfied the Rome III criteria for either IBS-C or FC.[1] No subjects had coexistent disease and all had normal hematology, biochemistry, urinalysis, and sigmoidoscopy, if indicated, together with a normal colonoscopy or barium enema if aged older than 40 years. Age- and sex-matched HVs were recruited by advertisement, and all had normal laboratory investigations, if indicated. Subjects were excluded if they had a history of gastrointestinal surgery (other than appendectomy and hiatus hernia repair); had gastrointestinal symptoms related to or exacerbated by consumption of milk or milk products; or were taking drugs that might modify either gastrointestinal function or the 5-HT system, such as analgesic medication, tranquilizers, or antidepressants. Apparent HVs were excluded if they had features suggestive of a functional bowel disorder, as assessed using the Rome III criteria. Females were excluded if they were pregnant, breastfeeding, or hysterectomized, and all were postpubertal and premenopausal. As there is evidence to suggest that steroid ovarian hormones might affect the 5-HT system,[18] abdominal symptoms,[19] visceral sensitivity,[20] and transit,[21] all females were studied during the luteal phase of the menstrual cycle (high progesterone and estrogen) or while taking combined (nonphased) estrogen/progesterone contraceptive medication. All medications and cigarette smoking were stopped for 48 hours before the study, and alcohol- and caffeine-containing products were prohibited 24 hours before the study. All subjects drank below the recommended safe alcohol limit (<21 units per week), smoked <10 cigarettes per day, and had not participated in a clinical trial of any drug within the previous 30 days. Written consent was obtained from all subjects and the study was approved by the South Manchester Medical Research Ethics Committee.

Study Protocol and Methods

All subjects completed a 7- to 9-day baseline symptom diary in which they scored the severity of their abdominal pain, bloating, and bowel urgency every evening using a 6-point scale (ranging from 0 [none] to 5 [very severe]) and indicated the time and consistency (7-point Bristol Stool Form Scale, ranging from 1 [hard lumpy] to 7 [watery diarrhea])[22] of any bowel movement. Symptoms associated with bowel movement, such as straining, urgency, and incomplete evacuation, were also assessed using the 6-point scale described here. In addition, subjects completed the Hospital Anxiety and Depression Scale questionnaire, from which anxiety or depression scores of >7 or combined score of >14 was considered abnormal.[23]

Subjects reattended the laboratory after an overnight fast and an arm vein was cannulated (day 1). Six-milliliter blood samples were taken via EDTA Vacutainer for 5-HT analysis at half-hour intervals for 2 hours under fasting conditions and for 4 hours after ingestion of a standard carbohydrate-rich meal, details of which have been published previously.[11,12,18] Symptomatology was assessed at hourly intervals throughout the study by asking the question "How would you rate your abdominal discomfort/pain and bloating over the last one hour?" using the 6-point scale.

After completion of the 5-HT study, subjects were given 3 differently shaped sets of radiopaque markers (24 of each) to take home and instructed to swallow them on consecutive days (days 2–4) as described previously.[24] Abdominal x-ray the following morning (day 5) allowed calculation of whole-gut transit time and segmental colonic transit using the method of Metcalf et al (see Data Collection and Statistic Analysis; Whole-gut [colonic] Transit Time section).[25] Subjects then returned to the laboratory for assessment of their oro-cecal transit time, as described by Levitt and the authors.[24,26]

Within 14 days of oro-cecal transit assessment, rectal sensitivity was assessed, as described in detail previously.[27] Briefly, this involved distending the rectum via a barostat (G&J Electronics Inc, Toronto, Canada) using the ascending method of limits followed by tracking for up to a total of 15 distensions or maximum of 56 mm Hg.[27,28] Subject feelings of "stool sensation" and "pain/discomfort" were scored using the following scales: Stool Sensation Scale, where 0 = no sensation, 1 = first sensation, 2 = constant sensation/gas, 3 = feeling of a need to