World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i2.384

World J Gastroenterol 2014 January 14; 20(2): 384-400
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

Is irritable bowel syndrome an organic disorder?

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Author contributions: El-Salhy M collected the literature data and wrote the manuscript; Gundersen D, Gilja OH, Hatlebakk JG and Hausken T contributed equally to discussions about the collected data and commented upon the manuscript; all of the authors approved the submitted version of the manuscript.
Supported by A grant from Helse-Fonna
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Received: September 27, 2013 Revised: November 5, 2013
Accepted: November 12, 2013
Published online: January 14, 2014

Abstract

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder that is generally considered to be functional because there appears to be no associated anatomical defect. Stress and psychological factors are thought to play an important role in IBS. The gut neuroendocrine system (NES), which regulates all functions of the gastrointestinal tract, consists of endocrine cells that are scattered among the epithelial cells of the mucosa, and the enteric nervous system. Although it is capable of operating independently from the central nervous system (CNS), the gut NES is connected to and modulated by the CNS. This review presents evidence for the presence of an anatomical defect in IBS patients, namely in the gastrointestinal endocrine cells. These cells have specialized microvilli that project into the lumen and function as sensors for the luminal content and respond to luminal stimuli by releasing hormones into the lamina propria, which starts a chain reaction that progresses throughout the entire NES. The changes in the gastrointestinal endocrine cells observed in IBS patients are highly consistent with the other abnormalities reported in IBS patients, such as visceral hypersensitivity, dysmotility, and abnormal secretion.

Key words: Cholecystokinin; Dysmotility; Endocrine cells; Enteric nervous system; Ghrelin; Peptide YY; Secretion; Secretin; Serotonin; Visceral hypersensitivity

Core tip: This review presents recent observations in irritable bowel syndrome (IBS) patients that point toward the existence of an anatomical defect in the gastrointestinal endocrine cells. It includes also an argument that IBS is an organic disorder and that the abnormalities in the gastrointestinal endocrine cells can explain the visceral hypersensitivity, dysmotility and abnormal secretion reported in these patients.

El-Salhy M, Gundersen D, Gilja OH, Hatlebakk JG, Hausken T. Is irritable bowel syndrome an organic disorder? *World J Gastroenterol* 2014; 20(2): 384-400 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i2/384.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i2.384

INTRODUCTION

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal disorder with a reported prevalence of 5%-20% and an incidence of about 200 per 100000 of the world population[1-29]. Patients with IBS suffer from recurrent abdominal pain/discomfort and altered bowel habit, which vary in both degree and time pattern between patients: from tolerable to severe, and from daily symptoms to intervals of weeks/months, respective-

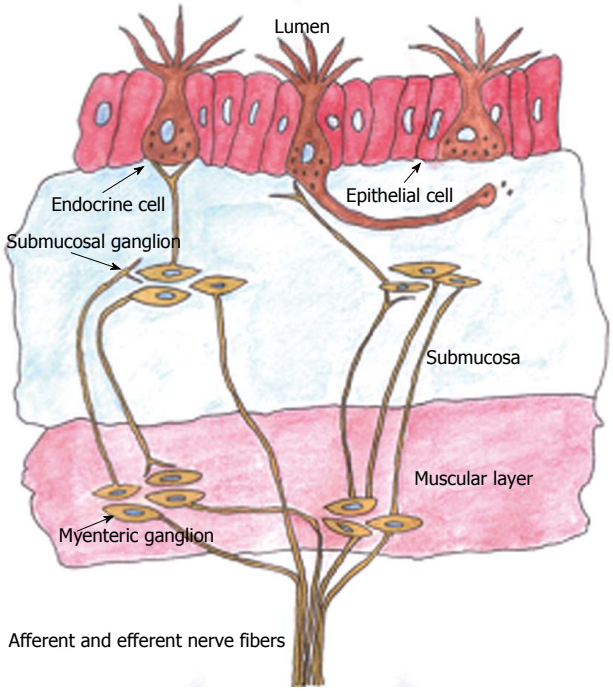

Figure 1 Schematic illustration of the gut neuroendocrine regulatory system. The endocrine cells are scattered among the epithelial cells and have specialized microvilli that project into the lumen and function as sensors of the gut contents, and they respond to luminal stimuli by releasing hormones into the lamina propria, where they exert their action locally on nearby structures. These endocrine cells interact with the enteric nervous system, which is in turn connected to and modulated by the central nervous system through afferent and efferent nerves.

ly[3,11,30-40]. IBS is more common in females than males, and in patients younger than 50 years of age[3,11,14,15,19,21,26,30,31,33-40].

IBS is not associated with the development of serious disease or with an excessive mortality rate[41,42]. However, it considerably reduces the sufferer's quality of life, interfering with their education, working ability and social life. Moreover, IBS represents an economic burden to both patients and society[23,43-49], since IBS patients visit their doctors more frequently, undergo more diagnostic tests, consume more medications, miss more workdays, are less productive at work, and are hospitalized more frequently than those without IBS[28,32,39,50-53].

There are no biomarkers for the diagnosis of IBS[54,55], which is instead based on the assessment of symptoms such as the Rome Ⅲ criteria[56,57]. IBS patients are subgrouped according to differences in the predominant bowel symptoms as IBS-diarrhea (D), IBS-constipation (C), IBS-both diarrhea and constipation (M), and non-subtyped IBS (patients with insufficient abnormality of stool consistency to meet the criteria for IBS-C, -D, or -M)[56,57]. The Rome criteria were introduced to facilitate positive diagnoses, reduce the costs due to unnecessary testing, and guide treatment; however, they fall short on these expectations and are generally neglected in clinical practice by both general practitioners and gastroenterologists[54,58-64].

IBS is considered to be a functional disorder in the absence of a known anatomic defect[65], the pathophysiology of which is incompletely understood. The pathogenesis appears to be multifactorial, with several factors suggested to play a role in the process, such as psychological factors, genetic factors, low-grade chronic intestinal inflammation, an abnormal gut neuroendocrine system (NES) and/or altered signaling in this system, dietary factors, and intestinal flora[66].

IBS patients can be roughly divided into two subsets: sporadic (nonspecific) and postinfectious (PI-IBS)/inflammatory bowel disease (IBD)-associated (IBD-IBS)[66]. Sporadic IBS includes patients who have had symptoms for a long time and without any associated events, in particular gastrointestinal or other infections. PI-IBS is defined as a sudden onset of IBS symptoms following gastroenteritis in individuals who have previously had no gastrointestinal complaints, and IBD-IBS is defined in IBD patients in remission who display IBS symptoms[66]. PI-IBS constitutes about 6%-17% of patients with IBS[67], and IBD-IBS occurs in 33%-46% of ulcerative colitis patients and 42%-60% of those with Crohn's disease[68-72].

This article summarizes the published findings on abnormalities in the gut neuroendocrine cells, discusses them in view of the currently known facts about IBS, and presents an argument for IBS being an organic gastrointestinal disorder.

GUT ENDOCRINE CELLS

The gut contains a large number of endocrine cells that are dispersed among the epithelial cells of the gut mucosa in all of the gut segments except for the esophagus[66,73-78]. These cells constitute the largest endocrine organ in the body and comprise about 1% of all epithelial cells in the gastrointestinal tract, where they are separated from one another by epithelial cells[73,74,79-81]. These cells have specialized microvilli that project into the lumen and function as sensors for the gut contents and respond to luminal stimuli by releasing hormones that, in general, target other parts of the digestive system (Figure 1)[82-94]. There are at least 15 different populations of endocrine cells in the gastrointestinal tract[60,73-76]. Some of them [including somatostatin and peptide YY (PYY) cells] have long slender cytoplasmic processes that project toward neighboring cells, increasing their paracrine effects (Figure 2)[95]. The distribution, functions, and modes of action of the most important endocrine/paracrine cells are given in Table 1[60,75,76,96-108].

Some of the different endocrine cell types are located in specific areas of the gut, while others (primarily somatostatin and serotonin cells) are found throughout the gut[73,74,76]. They secrete one or more signaling substances into the lamina propria, where they exert their action locally on nearby structures (autocrine/paracrine mode) and/or *via* an endocrine mode of action (by circulating in the blood to reach distant targets)[109]. These cells interact in an integrated manner with each other and with the enteric nervous system (ENS) and the afferent and efferent nerve fibers of the central nervous system (CNS), in particular the autonomic nervous system[60,76,99,110]. All of the cell types in the crypt/villus originate from pluripo-

Table 1 Overview of the main endocrine cells in the gastrointestinal tract

Cell content	Localization	Source of release	Actions
Serotonin (5-HT)	EC cells in the stomach, large and small intestines	Noradrenalin; acetylcholine; acidification and intraluminal pressure	Inhibits gastric emptying and stimulates colonic motility; accelerates small- and large-intestine transit activates the submucosal sensory branch of the enteric nervous system that conveys sensation from the gut to the central nervous system
Histamine	EC-like cells in the gastric oxyntic mucosa	Vagus nerve stimulation and inhibited by somatostatin	Stimulates gastric acid secretion
Somatostatin	The stomach, and large and small intestines	Mixed meal and acidification of the stomach	Inhibits intestinal contraction; inhibits gut exocrine and neuroendocrine secretion
Ghrelin	Gastric oxyntic mucosa	Protein and fat ingestion; suppressed by carbohydrate ingestion	Increases appetite and food intake; stimulates gastric and intestinal motility
Gastrin	Gastric antral mucosa	Intraluminal peptides; amino acids; calcium; amines; low pH and prostaglandins. Somatostatin inhibits release	Stimulates gastric acid secretion and histamine release; trophic action on gastric mucosa; stimulates contraction of the LES and antrum
CCK	Small intestine, especially the duodenum	Intraluminal protein and fat and inhibited by somatostatin	Inhibits gastric emptying; stimulates gallbladder contraction and intestinal motility; stimulates pancreatic exocrine secretion and growth; regulates food intake
Secretin	Small intestine, especially the duodenum	Acidification and inhibited by somatostatin	Stimulates pancreatic bicarbonate and fluid secretion; inhibits gastric emptying; inhibits contractile activity of the small and large intestines
GIP	Small intestine, especially the duodenum	Intraluminal glucose; amino acids and fat	Incretin action; inhibits gastric acid secretion
Motilin	Small intestine, especially the jejunum	Protein and fat ingestion	Induces phase-III migrating motor complex; stimulates gastric emptying; stimulates contraction of the LES
Neurotensin	Small intestine	Fat	Stimulates pancreatic section; inhibits gastric secretion; delays gastric emptying; stimulates colon motility
PYY	Terminal ileum and large intestine	Protein-rich meals	Delays gastric emptying; inhibits gastric and pancreatic secretion, stimulates the absorption of water and electrolytes; major mediator of the ileal brake
PP	Terminal ileum and large intestine	Protein-rich meals	Inhibits pancreatic secretion; stimulates gastric acid secretion; relaxes the gallbladder; stimulates motility of the stomach and small intestine
Enteroglucagon (oxyntomodulin)	Terminal ileum and large intestine	Intraluminal carbohydrates and fat	Inhibits gastric and pancreatic secretion; reduces gastric motility; has some incretin effect
Chromogranin	All gastrointestinal tract segments	Ingestion of a meal	Induces formation, sorting, and release of secretory granules of the gut endocrine/paracrine cells; an inflammatory mediator

CCK: Cholecystokinin; EC: Enterochromaffin; GIP: Gastric inhibitory peptide; LES: Lower esophageal sphincter; PP: Pancreatic polypeptide; PYY: Peptide YY.

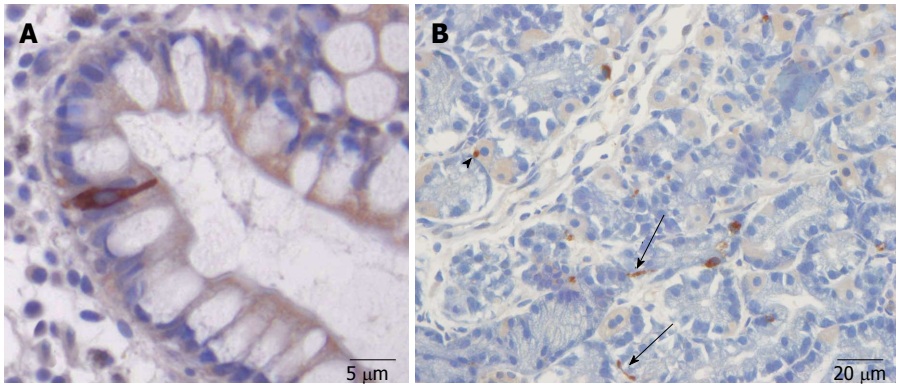

Figure 2 The gut endocrine cells. A: A chromogranin-A-immunoreactive endocrine cell in the ileum. The endocrine cell extends from the basal membrane of the mucosa that project into the gut lumen; B: Somatostatin-immunoreactive cells in the gastric oxyntic mucosa. Note the long cytoplasmic processes (arrows), which can occasionally be seen to end at the base of parietal cells (arrowhead).

tent stem cells of endodermal origin[73,74,111]. Each intestinal crypt contains four to six stem cells that differentiate into all epithelial cell types including enterocytes, goblet cells, Paneth cells, and endocrine cells[112-125]. These cells regulate several functions of the gastrointestinal tract, including sensation, motility, secretion, absorption, local

Table 2 Abnormalities in the densities of gastrointestinal endocrine/paracrine cells in patients with sporadic irritable bowel syndrome

Gastrointestinal segment	Endocrine cell type	IBS-D	IBS-M	IBS-C
Stomach				
Oxyntic mucosa	Ghrelin	High	Normal	Low
	Serotonin	High	Normal	Low
	Somatostatin	Low	Low	High
	Chromogranin A	Normal	Normal	High
Antrum	Serotonin	Normal	Low	High
	Gastrin	High	High	High
	Somatostatin	Low	Low	Low
	Chromogranin A	Normal	Low	High
Small intestine				
Duodenum	Serotonin	Normal	-	Normal
	CCK	Low	-	Normal
	Secretin	Low	-	Normal
	GIP	Low	-	Low
	Somatostatin	Low	-	Low
	Chromogranin A	Low	-	Low
Ileum	Serotonin	Low	Low	Low
	PYY	Normal	Normal	High
	Chromogranin A	Low	Low	Low
Large intestine				
Colon	Serotonin	Low	-	Low
	PYY	Low	-	Low
	Chromogranin A	Low	-	Low
Rectum	Serotonin	Normal	-	Normal
	PYY	Low	-	Low
	Enteroglucagon	Low	-	Low
	Somatostatin	High	-	High
	Chromogranin A	Normal	-	Normal

CCK: Cholecystokinin; PYY: Peptide YY; GIP: Gastric inhibitory peptide; IBS-C: Irritable bowel syndrome (IBS) with constipation as the predominant bowel symptom; IBS-D: IBS with diarrhea as the predominant bowel symptom; IBS-M: IBS with both constipation and diarrhea as the predominant bowel symptoms.

immune defense, and food intake (by affecting the appetite)[60,73,74,76,110].

ABNORMALITIES IN GUT ENDOCRINE CELLS IN IBS PATIENTS

Several abnormalities have been reported in all segments of the gastrointestinal tract of patients with IBS. As mentioned above, the endocrine cells exert their effects in part locally; however for some of them the endocrine mode of action is difficult to elucidate[99]. One example of this is the serotonin cells. The serotonin that they secrete is taken up into the blood and carried by platelets as they circulate through the gut[126-129]. Thus, the circulating serotonin is locked within the dense granules of the platelets, without any possibility of being delivered to distant targets. Therefore, summarizing and discussing abnormalities in the endocrine cells are considered separately herein relative to the various segments of the gastrointestinal tract.

Sporadic IBS

Abnormal endocrine/paracrine cells have been found in the stomach (Figure 3), proximal small intestine (duodenum), distal small intestine (ileum), colon (Figure 4), and rectum of patients with sporadic IBS[130-141]. These abnormalities manifest mostly as changes in the densities of these cells (*i.e.*, an anatomical defect). The abnormalities in the different endocrine cells in the various segments of the gastrointestinal tract of patients with sporadic IBS are summarized in Table 2. In addition to the abnormalities observed in the endocrine cells, there are alterations in the levels of serotonin transporter (SERT), which appear to be increased in the ileum and decreased in the rectum of IBS patients[130,141,142].

PI-IBS and IBD-IBS

Similar to sporadic IBS, abnormal endocrine/paracrine cell densities have been found in both PI-IBS and IBD-IBS. However, the nature of these abnormalities is different from those in sporadic IBS (Table 3)[141,143-150].

POSSIBLE ROLE OF GASTROINTESTINAL ENDOCRINE CELL ABNORMALITIES IN IBS

The mechanisms regulated by gastrointestinal endocrine cells include gut sensation, motility, and secretion. IBS patients exhibit visceral hypersensitivity, disturbed gastrointestinal motility, and abnormal gut secretion[65,107,151-153]. The degree to which the abnormalities in these cells observed in IBS patients contribute to these disturbed functions is discussed to below.

Visceral hypersensitivity

Visceral hypersensitivity has been demonstrated in the colorectal segment of IBS patients[154-161]. Hypersensitivity has also been reported in the esophagus, stomach, and small intestine[162-166]. However, visceral hypersensitivity is not present in all IBS patients, and a large prospective study found that only 20% of IBS patients showed hypersensitivity[167]. Furthermore, visceral hypersensitivity does not seem to be a panintestinal disorder[165]; IBS patients only appear to exhibit rectal hypersensitivity[159]. Whether the severity of abdominal pain is correlated with colorectal hypersensitivity in IBS remains a matter of controversy[154,156,168-172].

As mentioned above, serotonin cells have specialized microvilli that project into the gut lumen and act as sensors for the gut contents, and in particular for increased pressure. Serotonin is released in a regulated and calcium-dependent manner from serotonin cells into the surrounding tissues in response to luminal stimuli[173,174]. It activates the sensory branch of the ENS, which is localized in the submucosal plexus in the submucosa, and the myenteric plexus in between the smooth muscle fibers. These sensory branches convey sensation from the gut to the CNS through the sympathetic and parasympathetic nervous systems (Figure 1)[175-177]. The pain stimuli activate the cerebral cortex through the thalamus and permit the recognition of visceral pain[65,177]. Some studies have found IBS patients to be tolerant of somatic

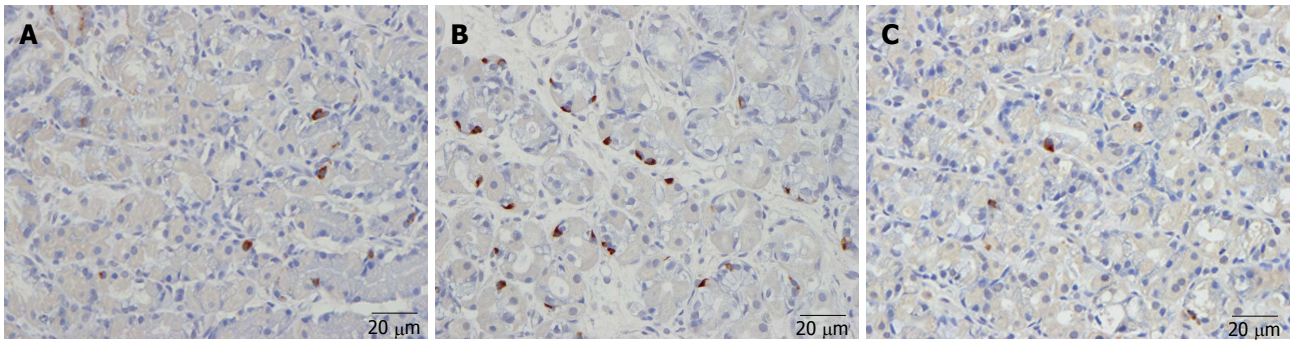

Figure 3 Ghrelin-immunoreactive cells. A: Ghrelin-immunoreactive cells in the gastric oxyntic mucosa of a healthy subject; B: In a patient with irritable bowel syndrome (IBS) with diarrhea as the predominant bowel symptom (IBS-D); C: In a patient with IBS with constipation as the predominant bowel symptom (IBS-C). The density of ghrelin cells is higher in IBS-D and lower in IBS-C than in the healthy control.

Table 3 Abnormalities in the densities of gastrointestinal endocrine/paracrine cells in patients with post infectious irritable bowel syndrome and inflammatory-bowel-disease-associated irritable bowel syndrome

Gastrointestinal segment	Endocrine cell type	PI-IBS	IBD-IBS
Small intestine			
Duodenum	Serotonin	High	-
	CCK	High	-
Large intestine			
	Serotonin	High	High/low
	PYY	High	Low
	PP	-	Low
	Enteroglucagon	-	High

CCK: Cholecystokinin; PYY: Peptide YY; PI-IBS: Post infectious irritable bowel syndrome; IBD-IBS: Inflammatory-bowel-disease-associated irritable bowel syndrome.

pain, and hence the hypersensitivity is confined to the viscera[158,165,178], while other studies found IBS patients to have a lower tolerance to somatic pain than healthy subjects[162,179,180]. Azpiroz *et al*[167] postulated that the exclusive visceral hypersensitivity experienced by some IBS patients could be attributable to abnormalities at the level of the gut, spinal cord, or brain, whereas patients with both visceral and somatic hypersensitivities have a disturbance above the gut level. Those authors also argued that a peripheral mechanism is involved in the visceral hypersensitivity in IBS.

The data presented in Table 2 suggest that none of the abnormalities in the gut endocrine cells could possibly contribute to the development of the visceral hypersensitivity seen in some sporadic IBS patients. However, it has been reported that SERT levels are increased in the ileum and reduced in the rectum of these patients[130,141,142]. The gut mucosa has a high SERT-producing capacity, since all of the epithelial cells lining the luminal surface of the gut express SERT[142,181]. A reduction in SERT results in impaired intracellular uptake and degradation in the gut epithelial cells, consequently increasing the availability of serotonin within the gut mucosa[182,183]. Considering that the serotonin cell density in sporadic IBS does not differ from that of a healthy subject, a decrease in SERT would markedly increase the amount of serotonin available at its receptors[141,142]. An increase in serotonin at the 5-hydroxytryptamine (5-HT)$_3$ receptors of the ENS sensory neurons would activate the sensory nerves, which would then transmit nociceptive information to the nervous system[99]. Conversely, duodenal and rectal serotonin cell densities are high in PI-IBS patients, possibly contributing to the development of visceral hypersensitivity.

Dysmotility

Dysmotility has been reported to occur in all segments of the gastrointestinal tract of patients with IBS, but mostly in the small and large intestines[151,153]. Some studies found lower pressures in the lower esophageal sphincter and abnormal esophageal contractions in IBS patients[184,185]; however, such esophageal motility abnormalities were not confirmed in other studies[186,187]. In addition, some authors have reported abnormal gastric emptying in patients with IBS[153,188-193], while others did not find any such abnormality in these patients[161,194-197]. It therefore seems that abnormalities of gastric emptying do not occur in all IBS patients. Furthermore, while IBS-C patients often exhibit delayed gastric emptying, rapid gastric emptying is found in IBS-D patients[155,189].

The ghrelin cell density in the gastric oxyntic mucosa is low and the serotonin cell density in the antrum of the stomach is high in IBS-C patients, while in IBS-D patients the ghrelin cell density in the gastric oxyntic mucosa is high and the densities of cholecystokinin (CCK) and secretin cells are reduced in the duodenum[132]. Ghrelin is a peptide hormone that was first isolated from the stomach, and originates mostly from endocrine cells in the oxyntic mucosa of the stomach, although small amounts are expressed in the small intestine, large intestine, and the arcuate nucleus of the hypothalamus[198-200]. Ghrelin has several functions, and plays a role in regulating the release of growth hormone from the pituitary gland, which increases appetite and feeding, and also plays a major role in energy metabolism[201-204]. Furthermore, ghrelin has been found to accelerate gastric and small- and large-intestine motility[83,110,205-214]. Serotonin acts on 5-HT$_{1p}$ receptors, which are located on a subset of inhibitory motor neurons of the myenteric plexus, relaxing the stomach *via*

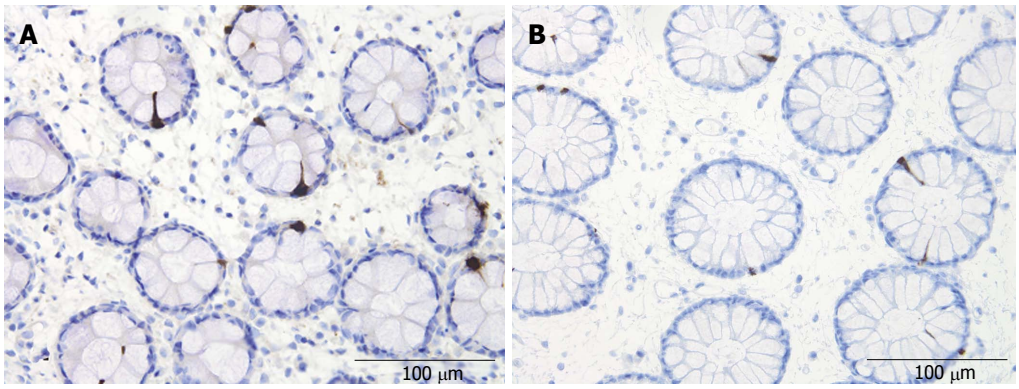

Figure 4 Peptide YY-immunoreactive cells. A: In the colon of a healthy subject; B: In a patient with irritable bowel syndrome (IBS). The density of peptide YY cells in the colon is lower in IBS patients than in healthy controls.

a nitrergic pathway and delaying gastric emptying[98,215-217]. CCK relaxes the proximal stomach in order to increase its reservoir capacity, and inhibits gastric emptying[218-220]. Secretin also inhibits gastric emptying[76,221]. It is therefore conceivable that low gastric ghrelin and high serotonin contribute to the slow gastric emptying in IBS-C, while the high gastric ghrelin and low intestinal CCK and secretin contribute to the rapid gastric emptying in IBS-D.

Several studies have found small-bowel transit to be delayed in IBS-C and accelerated in IBS-D[195,222-226]. However, a study from the Mayo clinic found no overall association between these IBS subgroups[161]. Studies on the motor patterns of the small bowel in IBS yielded contradictory results, which is probably due to marked inter- and intraindividual variations of small-intestine motor patterns[194,227-243]. As mentioned above, ghrelin cell density is low in the gastric oxyntic mucosa and PYY cell density is high in the ileum of IBS-C patients. Since ghrelin stimulates small-intestine motility and PYY stimulates the absorption of water and electrolytes, and is a major regulator of the ileal brake[244-249]. Moreover, it inhibits prostaglandin E2 and vasoactive intestinal polypeptide (which stimulate intestinal fluid secretion)[250-252], it is possible that the abnormalities in gastric ghrelin and ileal PYY contribute to the slow small-intestine transit in IBS-C. Secretin inhibits the contractile activity of the small intestine, and so the high ghrelin cell density and low duodenal secretin cell density may play a role in the rapid small-intestine transit in IBS-D.

It has been reported by some that colorectal transit is delayed in IBS-C and accelerated in IBS-D[153,222,223,253-258]. However, others have found that the colorectal transit time does not differ between IBS patients and controls[225,253,254]. The myoelectric and motor patterns of the large intestine of IBS patients have been investigated by several studies, which have yielded contradictory results[196,254-279]. In IBS-C, ghrelin cell density in the gastric oxyntic mucosa is low and ileal PYY cell density is high. Given that ghrelin stimulates intestinal motility and PYY stimulates the ileal-break, these abnormalities in ghrelin and PYY may promote the delayed colorectal transit observed in some IBS-C patients. CCK and secretin inhibit intestinal motility, and the cell densities of both are low in the duodenum of IBS-D patients. These factors together with a high gastric ghrelin cell density may contribute to the development of the accelerated colorectal transit seen in IBS-D patients.

In PI-IBS, the serotonin cell densities are high both in the small and large intestines, and CCK cell density is high in the small intestine. Serotonin primarily targets the mucosal projections of the intrinsic primary afferent neurons, which initiate peristaltic and secretory reflexes[156-161,175,280-289]. As mentioned above, CCK stimulates intestinal motility; thus, high serotonin and CCK levels could be responsible for the diarrhea seen in PI-IBS.

Abnormal secretion

Few studies have investigated gastrointestinal secretion in IBS patients. Enhanced intestinal secretion in response to bile acid perfusion in the ileum has been reported in these patients[290]. Increased reactivity of the secretory component of the migrating motor complex has been observed in the small intestine of IBS patients, and especially in those with IBS-D[291]. Among the abnormalities in the gut endocrine cells in IBS patients listed in Table 2, the low duodenal CCK and secretin observed in IBS-D, and the high ileal PYY cell density observed in IBS-C are particularly interesting with respect to gut secretions. CCK stimulates the secretion of digestive enzymes from pancreatic exocrine glands, and secretin stimulates pancreatic bicarbonate and fluid secretions[218,219]. The secretion of pancreatic bicarbonate increases the pH of the gut contents, which are highly acidic after leaving the stomach, and PYY stimulates the absorption of water and electrolytes[76]. This change in pH is essential for lipid digestion, since pancreatic lipase is irreversibly inactivated below pH 4.0[218]. It is tempting to speculate that IBS-D patients could suffer from fat maldigestion and a functional pancreatic insufficiency. Indeed, pancreatic enzyme substitution and a low-fat diet have been applied in clinical practice for these patients, with some success[292]. Moreover, an increase in PYY in the ileum of IBS-C patients may result in increased absorption of water from the feces, resulting in hard feces that worsen their to obstipation (Figure 4).

In conclusion, there are sufficient grounds to suspect

that the abnormalities in the gastrointestinal endocrine cells play a role in the development of visceral hypersensitivity, gastrointestinal dysmotility, and abnormal gastrointestinal secretion.

IS IBS AN ORGANIC DISORDER?

It has long been considered that IBS is caused by psychological stress and/or brain dysfunction, and it is overrepresented in patients with psychiatric illness/and or sexually and/or physically abused individuals. During the past decade there has been rapid progress in our understanding of IBS, and there is accumulating evidence of a biological etiology for this condition. Research to establish effective treatments for IBS have been intensified, and societal attitudes toward IBS patients are slowly changing.

This review presents evidence for an anatomic defect in IBS patients, namely the gastrointestinal endocrine cells. However, the data presented on the gastrointestinal endocrine cells in sporadic IBS were obtained by only two research groups. Further studies performed by other researchers involving different patient cohorts are needed before these observations can be confirmed. Conversely, while the data for PI-IBS were reported by several research groups from different countries and related to different patient cohorts, studies on PI-IBS have focused mainly on serotonin and are mostly restricted to the rectum. Further studies of other endocrine cells in different segments of the gastrointestinal tract are needed in PI-IBS. It should be noted that the gastrointestinal endocrine cells interact in an integrated manner with each other and the ENS, and together constitute the so-called neuroendocrine regulatory system of the gut[76,293-295]. It is thus possible that IBS patients have an abnormality in the ENS, in addition to those in the endocrine cells. However, investigating the ENS is very difficult since it would require whole-wall biopsy sampling under laparoscopic control, which represents a risk for both patients and controls. Regardless of the ethical issues this raises, it is unlikely that either patients or healthy subjects would voluntarily submit to laparoscopy and whole-wall biopsy sampling.

The abnormalities in the gut endocrine cells differ between sporadic IBS and PI-IBS/IBD-IBS, and their etiologies also appear to be different. Familial aggregation, twin, and genetic studies provide evidence for a genetic predisposition in sporadic IBS[296-306], and these patients describe their symptoms as commencing in childhood, suggesting the presence of genetically defective gastrointestinal endocrine cells. However, gastrointestinal mucosal cells - including the endocrine cells - have a rapid turnover, and it is also possible that factors related to luminal content such as diet or bacterial flora can provoke an increase or decrease in the endocrine cell population.

The etiology of the gastrointestinal endocrine cell abnormalities in PI-IBS and IBD-IBS appears to differ from that of sporadic IBS. Patients who develop PI-IBS and IBD-IBS likely have a genetic predisposition (host related) as well as other factors, such as infecting-organism-associated risk factors[307-315]. Following infection, these patients develop a low-grade inflammation that manifests as an increased intraepithelial and mucosal infiltration of lymphocytes and mast cells[143-149,316]. There is some evidence that inflammation and immune cells affect the gastrointestinal endocrine cells[317]. The secretion of serotonin by enterochromaffin (EC) cells can be enhanced or attenuated by the secretory products of immune cells, such as $CD4^+$ T, and also modulates the immune response[126,317]. The EC cells are in contact with or very close to $CD3^+$ and $CD20^+$ lymphocytes, and several serotonergic receptors have been identified in lymphocytes, monocytes, macrophages, and dendritic cells[318]. Therefore, it is conceivable that the abnormalities in the gastrointestinal endocrine cells in PI-IBS and IBD-IBS are caused by endocrine/immune interactions (*i.e.*, the endocrine/immune axis), which are in turn caused by low-grade inflammation in predisposed individuals[319,320].

CONCLUSION

The gut NES comprises the gastrointestinal endocrine cells and the ENS[76]. This regulatory system controls all gastrointestinal functions independently from the CNS[76,156]. However, the gut NES and the CNS are connected, and the CNS modulates the gastrointestinal functions through this connection[152]. Thus, a defect in the gut NES should be suspected in patients with IBS[76,294]. The gastrointestinal endocrine cells serve as chemical and mechanical transducers for afferent projections to the ENS, and subsequently to the CNS[294,321]. The present review describes evidence in the literature of an anatomic defect in the NES in IBS, namely defective gastrointestinal endocrine cells. Therefore, in line with some other gastroenterologists, we consider it highly likely that IBS is an organic disorder[107].

The endocrine cells interact in an integrated manner with each other. It is possible that the abnormality in many endocrine cells of the gut seen in IBS is caused by a defect in one or more endocrine cell types, which in turn results in changes in the other endocrine cell types.

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ISSN 1007-9327