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Irritable bowel syndrome: the role of gut neuroendocrine peptides

Magdy El-Salhy[1,2], Inge Seim[3], Lisa Chopin[3], Doris Gundersen[4], Jan Gunnar Hatlebakk[2], Trygve Hausken[2]

[1]Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, Norway, [2]Section for Gastroenterology, Institute of Medicine, Bergen University, Norway, [3]Ghrelin Research Group, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia, [4]Department of Research, Helse-Fonna, Haugesund, Norway

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1. ABSTRACT

Irritable bowel syndrome (IBS) is a common chronic disorder with a prevalence ranging from 5 to 10 % of the world's population. This condition is characterised by abdominal discomfort or pain, altered bowel habits, and often bloating and abdominal distension. IBS reduces quality of life in the same degree of impairment as major chronic diseases such as congestive heart failure and diabetes and the economic burden on the health care system and society is high. Abnormalities have been reported in the neuroendocrine peptides/amines of the stomach, small- and large intestine in patients with IBS. These abnormalities would cause disturbances in digestion, gastrointestinal motility and visceral hypersensitivity, which have been reported in patients with IBS. These abnormalities seem to contribute to the symptom development and appear to play a central role in the pathogenesis of IBS. Neuroendocrine peptides/amines are potential tools in the treatment and diagnosis of IBS. In particular, the cell density of duodenal chromogranin A expressing cells appears to be a good histopathological marker for the diagnosis of IBS with high sensitivity and specificity.

2. INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic condition that is characterised by abdominal discomfort or pain, altered bowel habits, and frequently bloating and abdominal distension. The degree of symptoms vary from tolerable to severe, and often interfere with daily activity (1). Estimates of prevalence of IBS varies from 12-30% , however recent diagnostic criteria, such as Rome criteria I, II or III, suggest that the IBS affects 5 to 10% of individuals worldwide (2-14). A cross-sectional population-based survey conducted in Norway using recent diagnostic criteria estimated that IBS affects 8,1% of the Norwegian population (15). IBS is more common in women than in men and more commonly diagnosed in patients younger than 50 years of age (2-14).

Conventional therapy for IBS has focused on symptomatic relief of symptoms such as pain, diarrhoea or constipation. Evidence of long-term benefit of pharmacological agents has been sparse and new agents which proved to be affective have raised issues concerning safety (16, 17). Not surprisingly, alternative therapies have been considered. Thus, cognitive behaviour therapy and

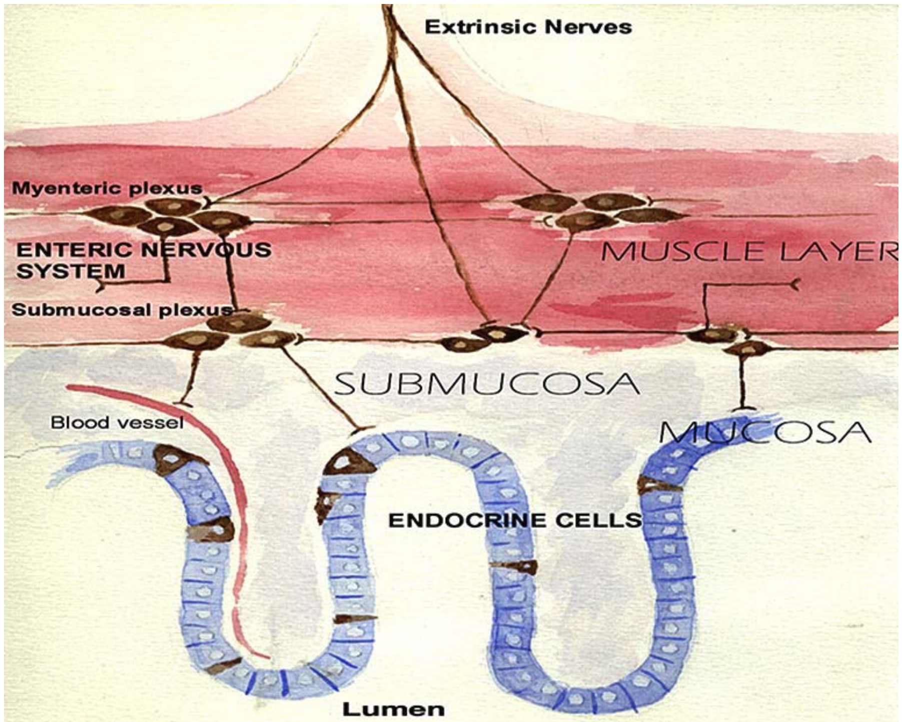

Figure 1. Schematic drawing to illustrate the neuroendocrine system of the gut.

gut-directed hypnotherapy have been used with good results (18). Other non- pharmacological approaches have been also tried with proven effect on symptoms and quality of life in patients with IBS (18). Reassurance and information to patients with IBS (19, 20), dietary management (21, 22), the administration of probiotics, and regular exercise have all been found, to reduce symptoms and improve quality of life of IBS patients (23-25).

IBS causes reduced quality of life to the same degree of impairment as major chronic diseases such as congestive heart failure, hepatic cirrhosis, renal insufficiency and diabetes (26-29). In an international survey of patients with IBS (30), patients with IBS reported impaired health status (restricting on average 73 days of activity in a year), poor health-related quality of life (particularly with dietary restrictions), mood disturbance, and interference with daily activity. Astonishingly, and illustrating the psychological toll of the condition, this survey showed that IBS patients would give up 25% of their remaining life (average 15 years) and 14% would risk a 1/1000 chance of death to receive a treatment that would make them symptom-free.

Although a minority (10-50%) of IBS patients seeks healthcare, they generate a substantial workload in both primary and secondary care (6-8). It is estimated that 12-14% of primary care patient visit, and 28% of referrals to gastroenterologists are IBS patients, making this a more common reason for a visit to physician than diabetes, hypertension or asthma (31-33). Not only do IBS patients visit their doctors more frequently, but more diagnostic tests are also performed, and they consume more medications, miss more workdays, have low work productivity, are hospitalised more frequently, and incur more overall direct costs than those without IBS (6, 14, 34, 35). The annual costs in USA (both direct and indirect) to manage patients with IBS are estimated at 15-30 billion USD (6, 34, 35).

Disturbances in gastrointestinal motility and visceral hypersensitivity have been reported in patients with IBS (11-49). It has been speculated that this dysmotility and hypersensitivity is caused by genetic, psychosocial factors and stress (13). The neuroendocrine peptides/amines of the gastrointestinal tract play an important role in regulating gastrointestinal motility and visceral sensitivity (see the next section). Thus, this review will shed light on the role of the gut neuroendocrine peptides in the pathogenesis, diagnosis and treatment of IBS.

3. THE NEUROENDOCRINE PEPTIDES OF THE GUT

A century ago, Pavlov proposed that the central nervous system alone controlled the gastrointestinal tract. Since then, another local control mechanism has been discovered, that is able to control the gut without any central nervous system involvement. This system, called the neuroendocrine system of the gut (NES) consists of two parts: endocrine cells scattered among the epithelial cells of the mucosa facing the gut lumen, and peptidergic and serotonergic as well as nitric oxide-containing-nerves of the enteric nervous system in the gut wall (Figure 1) (50).

Table 1. Overview of the main neuroendocrine peptides/amines in the gastrointestinal tract

Peptide/amine	Amino acid residues	Mode of action	Cellular origin	Action	Released by:
Pancreatic polypeptide (PP)	36	Endocrine	Intestinal PP-cell	Inhibits, pancreatic secretion; stimulates gastric acid secretion; relaxes the gallbladder and stimulates motility of the stomach and small intestine.	Protein rich meals.
Neuropeptide Y (NPY)	36	Transmitter, mediator	Myenteric and submucosal neurones	Inhibits pancreatic and intestinal secretion; decreases gastrointestinal motility; and is a vasoconstrictor.	Protein rich meals.
Peptide YY (PYY)	36,34	Endocrine, paracrine	Intestinal H/L cell	Delays gastric emptying; inhibits gastric and pancreatic secretion; and is major ileal brake mediator.	Protein rich meals.
Motilin	22	Endocrine	Intestinal M-cell	Induces phase III MMC (migrating motor complex); stimulates gastric emptying and stimulates contraction of LES.	Protein and fat ingestion.
Ghrelin	28	Endocrine	Gastric oxyntic X/A cell	Ghrelin increases appetite and feeding; stimulates gastric and intestinal motility.	Protein and fat ingestion and suppressed by carbohydrate ingestion.
Gastrin	17,34	Endocrine	Gastric G-cell	Stimulates gastric acid secretion and histamine release; trophic action on gastric mucosa; and stimulates contraction of lower oesophageal (LES) and antrum.	Intraluminal peptides; amino-acids; calcium; amines; low pH and prostaglandins. Somatostatin inhibits release.
Cholecystokinin (CCK)	8,33,39,58	Endocrine Transmitter?	Intestinal I-cell, myenteric and submucosal neurones	Inhibits gastric emptying; stimulates gallbladder,contraction and intestinal motility; stimulates pancreatic exocrine secretion and growth; and regulates food intake.	Intraluminal protein and fat and inhibits by somatostatin.
Secretin	27	Endocrine	Intestinal S-cell	Stimulates pancreatic bicarbonate and fluid secretion; inhibits gastric emptying; and inhibits contractile activity of small and large intestine.	Acidification and inhibited by somatostatin.
Gastric inhibitory peptide (GIP)	42	Endocrine	Small intestinal cells	Incretin; and inhibits gastric acid secretion.	Intraluminal glucose; amino-acids and fat.
Vasoactive polypeptide (VIP)	28	Transmitter, mediator	Myenteric and submucosal neurones	Stimulates gastrointestinal and pancreatic secretion; relaxes smooth muscles in the gut and causes vasodilation.	Serotonin.
Enteroglucagon	69	Endocrine	Intestinal L-cell	Inhibits gastric and pancreatic secretion.	Intraluminal carbohydrates and fat.
Somatostatin	14, 28	Paracrine, endocrine	Gastric and intestinal D-cell, myenteric and submucosal neurones	Inhibits intestinal contraction; and inhibits gut exocrine and neuroendocrine secretion.	Mixed meal and acidification of the stomach.
Neurotensin	13	Endocrine, transmitter, mediator	Intestinal N-cell, myenteric and submucosal neurones	Stimulates pancreatic section; inhibits gastric secretion; delays gastric emptying; and stimulates colon motility.	Fat
Galanin	30	Transmitter, mediator	Myenteric and submucosal neurones	Inhibits gastric, pancreatic and intestinal secrtion; delays gastric emptying and intestinal transit; and suppresses postprandial release of some neuroendocrine peptides.	Fat
Substance P	11	Transmitter, mediator	Myenteric and submucosal neurones	Stimulates smooth muscle contraction; vasodialator and inhibits gastric acid secretion.	Gut distention
Serotonin (5 hydroxit-ryptamine)	amine	paracrine, mediator, transmitter	Enterochromaffin (EC) cells, myenteric and submucosal neurones	Simulates gastric antrum and small intestine as well as gastric empyting and both colonic motility; accelerates small intestinal and large intestinal transit.	Noradrenalin; acetylcholine; acidification and intraluminal pressure.
Nitric oxide (NO)	gas	Transmitter	Myenteric and submucosal neurones	Relaxation of smooth muscle	Activation of protein kinase C alpha and/or epsilon

This system regulates several functions of the gastrointestinal tract, such as motility, secretion, absorption, microcirculation of the gut, local immune defence and cell proliferation (51-60). This regulatory system includes a large number of neuroendocrine peptides/amines (Table 1). These bioactive substances exert their effects through an endocrine mode of action (by circulating in the blood to reach a distant targets), by autocrine/paracrine mode (local action), by synaptic signalling, or by neuroendocrine means (through release into the circulating blood from synapses). The different parts of this system interact and integrate with each other, and with afferent and efferent nerve fibres of the central nervous system, in particular the autonomic nervous system.

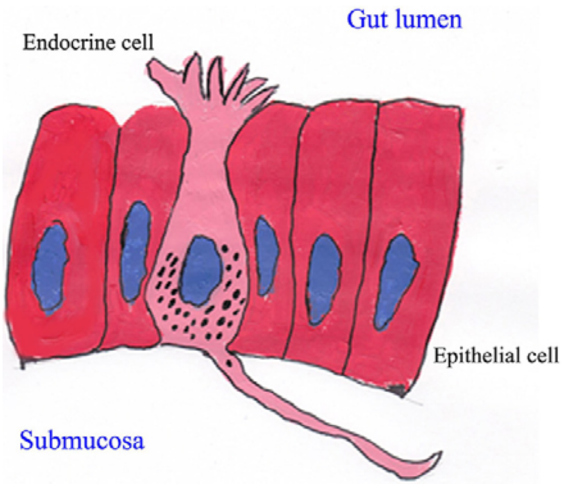

Figure 2. Schematic illustration of the endocrine/paracrine cell in the gut.

Endocrine/paracrine cells are scattered between the epithelial cells in the gut (Figure 2). They are often flask- or basket shaped, with a broad base, while the apical part of the cell reaches the gut lumen. Some of these cells (including somatostatin and efficient (e.g. somatostatin and PYY cells). Different endocrine/paracrine cell types are located in specific areas of the gut, while others (primarily somatostatin and serotonin cells) are found throughout the gut, namely. All cell types in one crypt/villus originate from a pluripotent stem cells of the endodermal origin. This means that entrocytes, Goblet cells, Paneth cells and endocrine/paracrine cells in one crypt/villus are of monoclonal origin (61).

The enteric nervous system consists of neurones which have cell bodies located in the gut wall. The peptidergic neurones (including serotonin neurones) are considered to be a part of the NES. There are two main nerve plexuses in the gut, the myenteric plexus (or Aurebach`s plexus) located between the longitudinal and the circular muscle layers in the entire gastrointestinal tract, and the submucosal plexus (or Meissner`s plexus) between the submucosa and the circular muscle. Neurones from the myenteric ganglia project predominantly to the muscle layer, but also to the mucosa, the submucosal plexus and to the other myenteric ganglia. The myenteric plexus contains most of the neurones involved in motility and gastric acid control. Neurones from the submucosal ganglia project predominantly to the mucosa , but also to myenteric ganglia, the circular muscle layer and other submucosal ganglia. These neurones are involved in the control of mucosal fluid transport and vasodilator reflexes. The ganglia of the two plexuses are connected to a continuous meshwork; the meshwork of the myenteric plexus is more regular. The enteric nervous system receives some input from the central nervous system, but most input comes from other enteric neurones. More than gut 20 neuropeptides have been identified in addition to classical transmitters such as acetylcholine, noradrenalin and serotonin. The neurotransmitter action of these has only been established for a few of these neuropeptides. Many neuropeptides and neurotransmitters are co-localised in the same neurones and one bioactive substance may have different effects in different parts of the gut (61).

4. THE POSSIBLE ROLE OF THE GUT NEUROENDOCRINE PEPTIDES/AMINES IN THE PATHOGENESIS OF IBS

The available data on the neuroendocrine system of the gut in patients with IBS, mainly describe the endocrine/paracrine cells in the mucosa, as the mucosa is easily biopsied during standard endoscopic procedure performed in these patients. Investigation of the enteric nervous system is considerably more difficult as this would require whole wall biopsies to be taken under laparoscopy and this procedure is associated with an increased risk for the patients. This procedure can be risky. Moreover, besides the ethical issues this raises, few patients are willing to volunteer to undergo laparoscopy.

Ghrelin is a 28-amino acid peptide hormone, which was isolated from the stomach (62), may play a role in the pathogenesis of IBS. Ghrelin originates mostly from endocrine cells in the oxyntic mucosa of the stomach but small amounts were found in both the small intestine and arcuated nucleus of the hypothalamus (62, 63). Ghrelin has several functions, the most known is its growth hormone(GH)-releasing effect in the pituitary, where it acts synergistically with GH-releasing hormone (63, 64). Ghrelin also increases appetite and feeding and plays a major role in energy metabolism (65, 66). Furthermore, ghrelin has been found to accelerate gastric as well as small- and large intestinal motility (67-77). Ghrelin may also have anti-inflammatory actions and protect the gut against a wide range of insults. In the stomach of patients with IBS, the density of ghrelin-immunoreactive cells in the oxyntic mucosa was significantly lower in IBS-constipation and significantly higher in IBS-diarrhoea patients than healthy controls (Figures 3 and 4) (78). Unexpectedly, the levels of total or active ghrelin in plasma and the stomach tissue extracts of IBS patients did not differ from that of healthy subjects (78, 79). Although ghrelin cell is increased in IBS-diarrhoea patients, the synthesis and release of ghrelin may be downregulated in these patients in order to compensate. Conversely, ghrelin cell density is decreased in IBS-constipation patients, ghrelin synthesis and release must be upregulated. One can hypothesise that this compensatory mechanism is influenced by fatigue with subsequent intermittent diarrhoea or constipation seen in IBS-patients (78).

The density of neuropeptide expressing cells is altered in the small intestine of IBS patients. Thus, the density of cells expressing gastric inhibitory polypeptide (GIP) and somatostatin is decreased in patients with IBS with both diarrhoea- and constipation-predominant subtypes (80). The cell densities of secretin and cholecystokinin (CCK) expressing cells are decreased in the diarrhoea-predominant subtype, but not in the

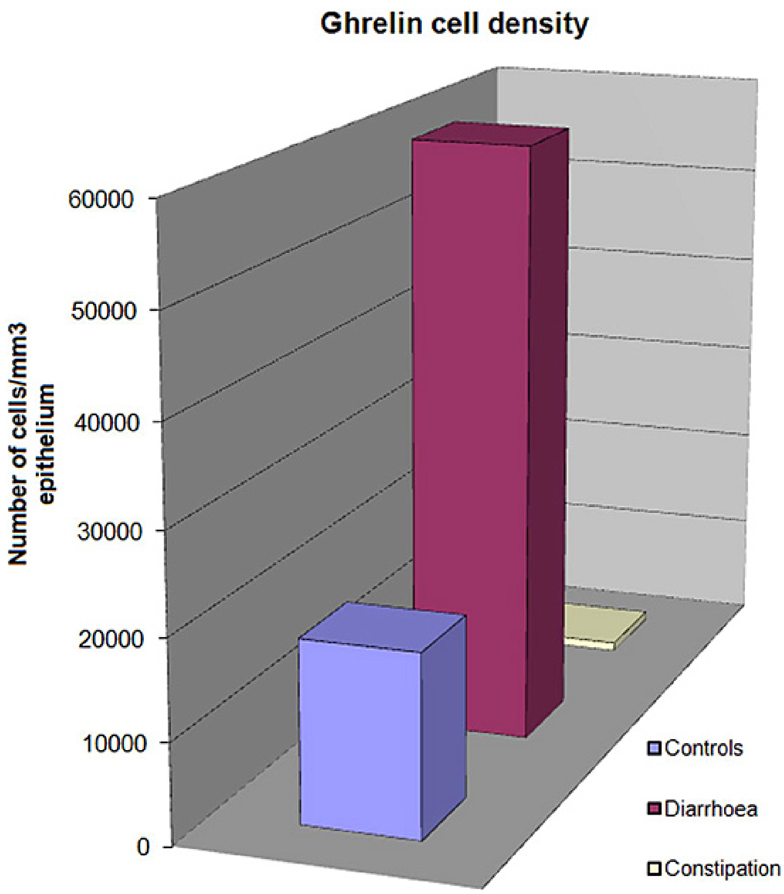

Figure 3. Ghrelin cell density in the oxyntic mucosa of controls, IBS-diarrhoea and IBS-constipation

constipation-predominant subtype (Figures 5 and 6). Serotonin cell density has been found to be unchanged in the duodenum of IBS patients, regardless the subtype (80-82). These peptides all play an important role in secretion and gastric motility.

As secretin, GIP and somatostatin inhibit gastric acid secretion (57, 58). The reduced density of these cells in the small intestine of IBS patients may result in elevated gastric acid secretion. This could contribute to the high incidence of dyspepsia in IBS patients. Secretin also stimulates pancreatic bicarbonate and fluid secretion (57, 58). The secretion of pancreatic bicarbonate increases the pH of the gut contents, which is highly acidic after leaving the stomach, and this is essential for lipid digestion as pancreatic lipase is irreversibly inactivated below pH 4.0 (83). CCK is released in response to nutrients and fatty acids in particular (84, 85). CCK relaxes the proximal stomach to increase its reservoir capacity, inhibits gastric emptying, stimulates gall bladder contraction and pancreatic exocrine secretion of digestive enzymes from pancreatic exocrine glands (83). As secretin and CCK cell densities are low IBS-diarrhoea patients, they would be to demonstrate rapid gastric emptying. It is conceivable that these patients could exhibit a functional pancreatic insufficiency and inadequate emptying of the gall bladder. Indeed, pancreatic enzymes substitution and low fat-diet have been applied in clinical practice to these patients with some success. Furthermore, as secretin inhibits gastric emptying and intestinal motility (57, 58), low levels of secretin and CCK may contribute to accelerated gastrointestinal motility and ultimately diarrhoea in these patients. It is noteworthy that in IBS which occurs after acute Giardiasis infection, the number of CCK and serotonin cells have been reported to be increased (86).

In the large intestine, serotonin and polypeptide YY(PYY) cell densities have been found to be low in both IBS-constipation and IBS-diarrhoea patients (Figures 7 and 8) (87). About 95% serotonin in the body is expressed in the gastrointestinal tract and is synthesised by enterochromaffin (EC) cells and sertonergic neurones of the myenteric plexus (88). Serotonin acts on 5-HT_{1p} receptors, which are located on a subset of inhibitory motor neurones of the myenteric plexus (89, 90). It relaxes the stomach through a nitrergic pathway and delays gastric emptying (91-93). Serotonin secreted by EC cells primarily targets the mucosal projections of primary afferent neurones. These include extrinsic nerves (94-98), which transmit the sensation of nausea and discomfort to the central nervous system, and the mucosal projections of intrinsic primary afferent neurones, which initiate peristaltic and secretory reflexes (99-104). The secretion of serotonin by myenteric neurones mediates fast and slow

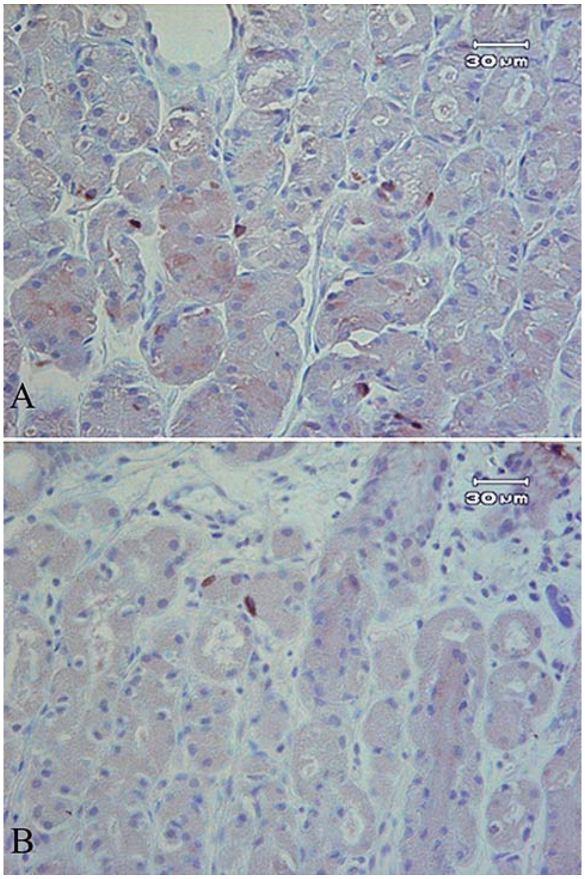

Figure 4. Ghrelin in oxyntic mucosa of a healthy subject (A) and in a IBS-C patient (B).

excitatory neurotransmission and is involved in regulating gastrointestinal motility (105). Serotonin stimulates secretion of chloride and water from small intestine by acting through the 5-HT_3 and 5-HT_4 receptors (106, 107). PYY stimulates the absorption of water and electrolytes and is a major regulator of the "ileal brake" (108-110). The low density of serotonin cells would be likely to reduce motility of the colon in patients with IBS. Low levels of PYY would consequently cause rapid passage from the ileum to the colon and result in watery faeces. As hypothesised, compensation for low cell number may occur through an increase in the cellular synthesis and release of these hormones could result in normal bowel movement in these patients. When this compensator mechanism is affected by fatigue, however, constipation would occur if serotonin secretion was affected, or diarrhoea would occur if PYY secretion was affected (86). It is noteworthy, that in patients with post-infectious IBS of the diarrhoea predominant type, the number of serotonin cells has been increased in the rectum (111-114).

The abnormalities in the gastrointestinal endocrine cells in IBS patients could be primary or secondary to other pathological process. Thus, primary genetic defect(s) could be responsible for the previously mentioned changes in the gut endocrine cells. In support of this assumption is the finding of an association between a functional polymorphism in the serotonin transporter (SERT) gene and diarrhoea predominant IBS (115, 116). These abnormalities can also be secondary to a mucosal subclinical inflammation (117, 118). In favour of this argument is the recent findings of an interaction of the gut neuroendocrine peptides/amines and the local immune system in the gut so called endocrine/immune axis. Thus, chromogranin-derived peptides such as chromofugin and vasostatin-I are able to penetrate into polymorphonuclear neutrophils, inducing an extracellular calcium entry (118). This study illustrates the role of chromogranins in active communication between the neuroendocrine and immune system. Moreover, Chromogranin-derived peptide, catestatin stimulates chemotaxis of human peripheral blood monocytes (119, 120). Secreoneurin, a Chromogranin-derived peptide reduces IL-6 release from eosinophils (120). Furthermore, chromogranin-derived peptides modulate the endothelial permeability during inflammatory process. Chromogranin A prevents the vascular leakage induced by tumour necrosis factor (TNF)-alpha in a mouse model (121). Serotonin secretion by enterochromaffin (EC) cells can be enhanced or attenuated by secretory products of immune cells such as CD4+T (122). Furthermore, serotonin modulates the immune response (118). The EC cells are in contact with or very close to CD3+ and CD20+ lymphocytes and several serotonergic receptors have been characterized in lymphocytes, monocytes, macrophages and dendrtic cells (118). Moreover, immune cells in the small- and large intestine exhibit receptors for substance P and vasoactive intestinal polypeptide (VIP) (123).

From the previous presentation, abnormalities have been reported in the neuroendocrine peptides/amines of the gut. These abnormalities would cause disturbances in digestion, gastrointestinal motility and visceral hypersensitivity. All these disturbances have been reported in patients with IBS (11, 36-49). While, it can be argued that the abnormalities observed in the neuroendocrine peptides/amines in IBS patients be primary or to secondary to other disorders. These abnormalities nevertheless contribute to the symptom development and appear to play a central role in the pathogenesis of IBS.

5. THE GUT NEUROENDOCRINE PEPTIDES/AMINES AS A TOOL IN THE DIAGNOSIS OF IBS

There is no biochemical, histopathological or radiological diagnostic test for IBS. Rather, the diagnosis of IBS is based on symptom assessment such as Rome criteria III (124), and exclusion of warnings symptoms such as weight loss, rectal bleeding, and the presence of markers for inflammation or infections. IBS patients are sub-grouped on the basis of differences in predominant bowel pattern as diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C), or a mixture of both diarrhoea and constipation (IBS-M). Therefore, it is, therefore, difficult sometimes to distinguish clinically IBS from adult-onset celiac disease (125-130), inflammatory bowel diseases, especially with mild disease activity (125, 131, 132), or microscopic colitis (133)

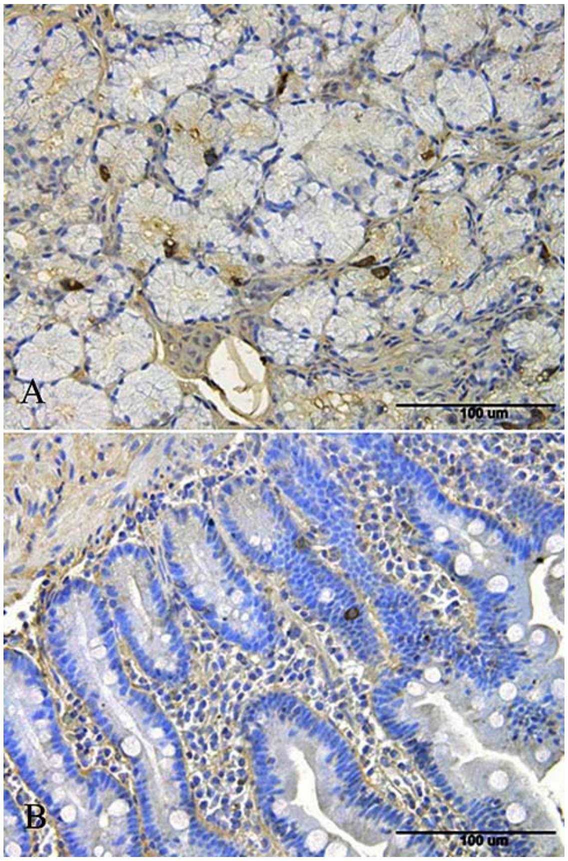

Figure 5. Cholecystokinin immunoreactive cells in the duodenum of a healthy subject (A) and of a patient with IBS-diarrhoea (B).

Chromogranin A-containing cell density is low in the duodenum and colon of both IBS-constipation and IBS-diarrhoea patients (Figures 9-11) (134). As chromogranin A is a general marker for endocrine cells, this finding indicates that a general reduction in small intestinal endocrine cells does occur in these patients (135-137).

It has been proposed that the quantification of chromogranin A cell density could be used as a histopathological marker for the diagnosis of IBS (135). Receiver-operator characteristic (ROC) curves for chromogranin A cell density in the duodenum and colon are given in Figure 12. The sensitivity and specificity at the cut off < 31 cells/mm^2 in the duodenum are 91 and 89%. In the colon the corresponding figures with a cut off <30 cells/mm^2 are 81 sensitivity and 88% specificity. It is noteworthy, that these results are based on 41 patients and 42 controls for the duodenum and 41 patients and 17 controls in the colon. A study of a larger number of patients and control subjects is ongoing. Importantly, however, these results demonstrate that chromogranin A cell density has a higher sensitivity and specificity in the duodenal tissue than in colon specimens. This may be due to the fact that the duodenum harbours almost all the endocrine cell types expressed by the small intestine and in a large number (138). Furthermore, it is much easier, more acceptable for the patients if duodenal biopsies are obtained by gastroscopy, rather than obtaining colon biopsies using colonoscopy with biopsies. AS duodenal biopsies provide more sensitive and specific results, this method would be preferred over the collection analysis of colonic biopsies to determine chromogranin A cell density. Screening of IBS patients for celiac disease is now an widely accepted (139). Thus, gastroscopy with duodenal biopsies can be used for excluding or confirming celiac disease instead for blood tests and the same biopsies can be used for the diagnosis of IBS.

6. THE GUT NEUROENDOCRINE PEPTIDES/AMINES USE IN THE TREATMENT OF IBS

The neuroendocrine peptides/amines of the gut have a potential to be used in the treatment of IBS. This may be considered as a correction of pre-existing abnormality or a use of their pharmacological actions. The problem in using the neuroendocrine peptides/amines of the gut as drugs is that they, by their very nature, have broad physiological/pharmacological effects. They can often bind to and activate several receptors with independent actions. Thus, in order to be able to target these bioactive substances, receptor-specific agonists or antagonists should developed. Among these serotonin agonists and antagonists have proved to be useful in clinical practice. There are seven different families of 5-HT (serotonin) receptors and 21 different subtypes. Most of these receptors occur in the central nervous system. In the gut only 5-HT receptors, 5-HT$_1$, 5-HT$_3$ and 5-HT$_{4,}$ are widely expressed (140-142).

5-HT$_1$ receptors are expressed by a subset of inhibitory motor neurones of the myenteric plexus of the stomach (92, 143). Sumatriptan, a gastric 5-HT$_{1p}$ receptor agonist for the, relaxes the stomach and delays gastric emptying for solids and liquids (93, 95, 144). Buspirone and R137696 are 5-HT$_1$ receptor agonists with a similar effects as sumatriptan (145-147). These agonists have been found to improve symptoms of early satiety in dyspeptic patients with impaired accommodation (148, 149). This 5-HT receptor does not seem to be clinically relevant as a target for treatment of IBS patients, however.

Ondansetron, granisetron, alosteron, and cilansetron are 5-HT$_3$ receptor antagonists (88). These antagonists have been found to decrease small intestinal secretion, small and large intestinal motility, nausea and to reduce colonic hypersensitivity (150-156). Alosteron was approved for the treatment of IBS-diarrhoea in female patients (157-161). This drug was, withdrawn from the market, however, because of its side-effects (162). Other 5-HT$_3$ receptor antagonists, especially cilansetron, have been investigated or are underdevelopment for treating IBS-diarrhoea patients (154-164). 5-HT$_3$ receptor agonists have no therapeutic values because of their role in signalling nociceptive information , such as nausea from the bowel to the central nervous system (88).

5HT$_4$ receptors are located on afferent neurones in the myenteric plexus, smooth muscles and enterochromaffin cells (165, 166). These receptors mediate

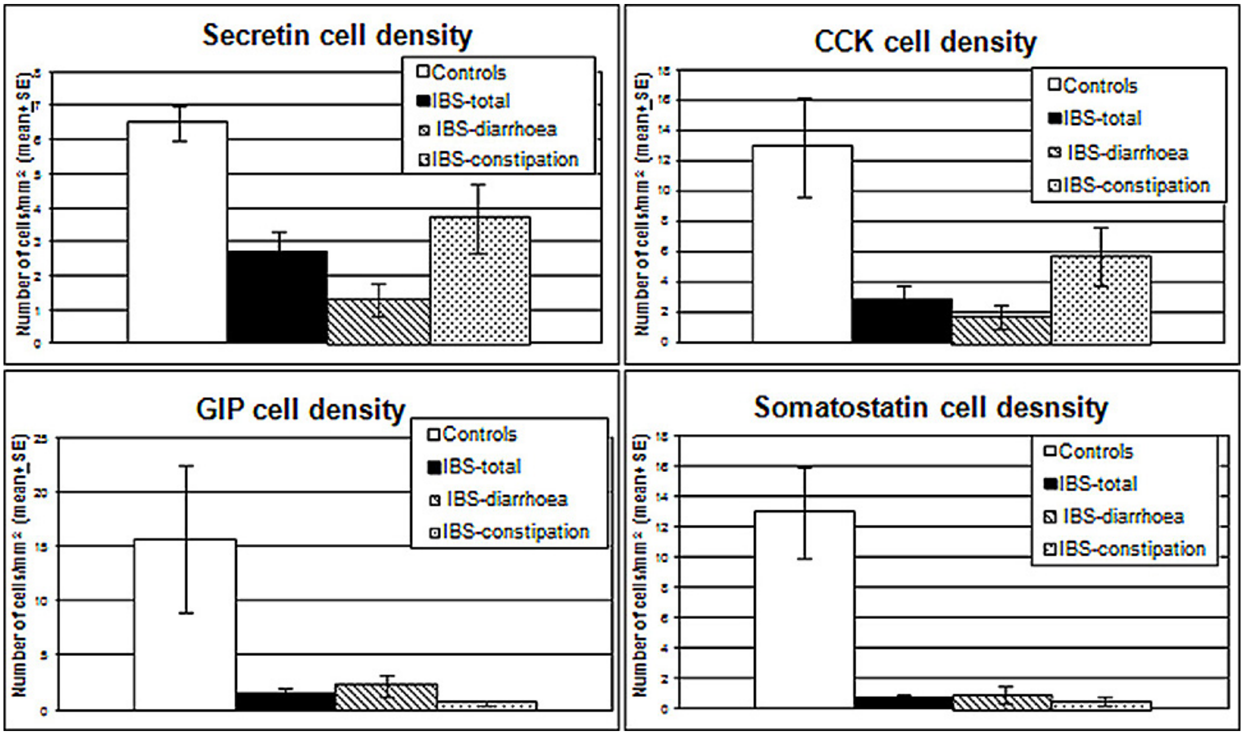

Figure 6. Secretin, CCK, GIP and somatostatin cell densities in the duodenum of controls and IBS patients.

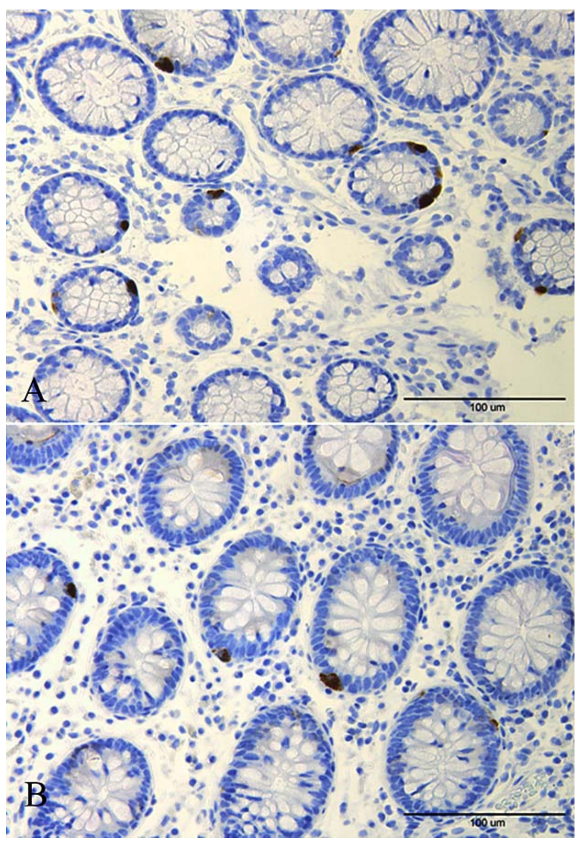

Figure 7. Serotonin cells in the colon of a healthy control (A) and in a patient with IBS (B).

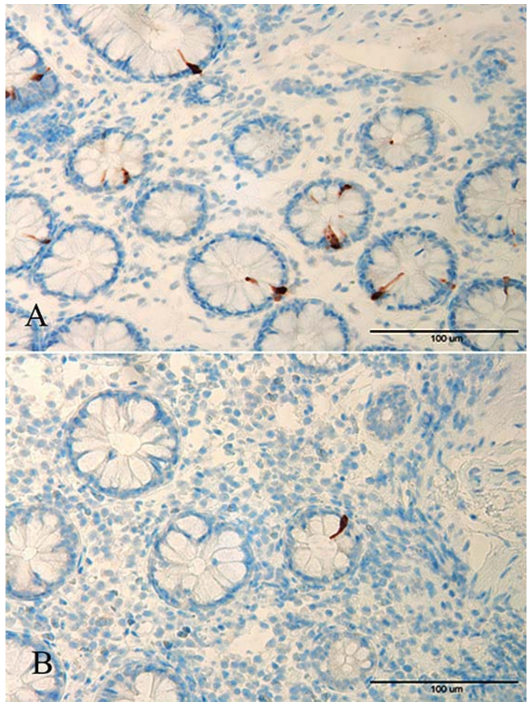

Figure 8. PYY immunoreactive cells in the colon of a healthy subject (A) and of an IBS patient (B).

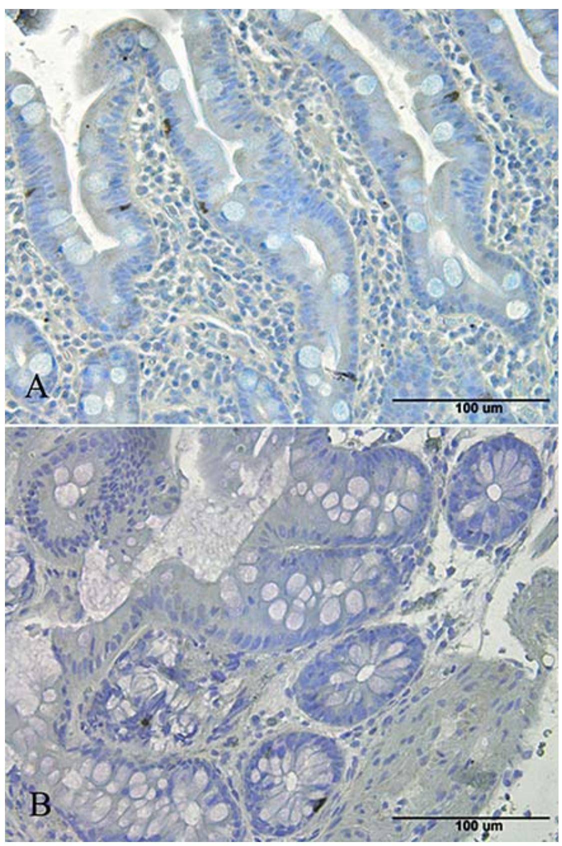

Figure 9. Chromogranin A positive cells in the duodenum of a healthy subject (A) and of a patient with IBS (B).

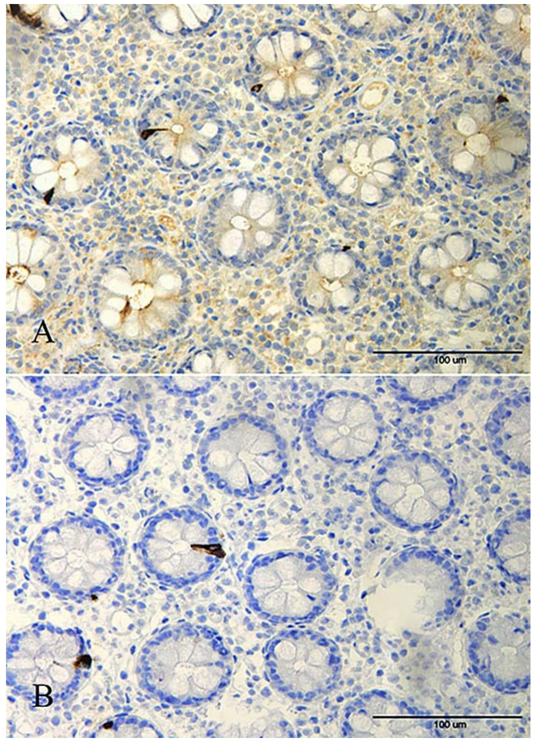

Figure 10. Chromogranin A immunoreactive cells in the colon of a healthy subject (A) and of a patient with IBS (B).

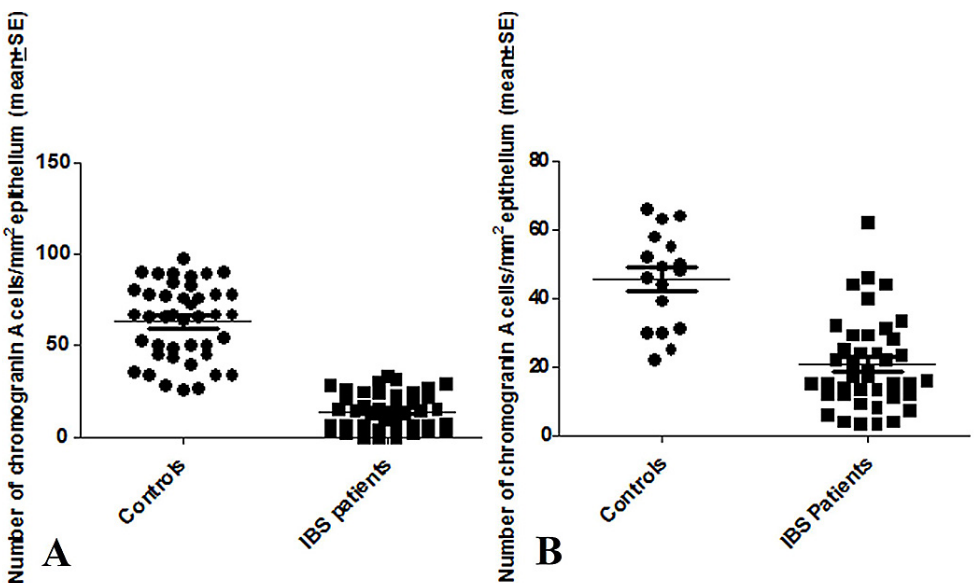

Figure 11. Chromogranin A cell density in the duodenum (A) and in the colon (B) of controls and IBS patients.

the release of the colonic neurotransmitters acetylcholine, substance P, vasoactive intestinal polypeptide (VIP) and calcitonin- gene-related peptide, which stimulates the peristaltic reflex (167). Furthermore, $5HT_4$ receptor activation induces small bowel and colonic fluid secretion (168-170). Tegaserod, prucalopride, renzapride and cisapride are $5HT_4$ receptor agonists (88). Tegaserod has been shown to promote small intestinal transit time and to enhance proximal colonic emptying in IBS-constipation patients (171). In healthy humans, tegaserod stimulates intestinal secretion and promotes evacuation of jejunely perfused gas (109, 172, 173). Tegaserod has been used in the treatment of IBS-constipation, but it has been withdrawn from the market because of the side-effects (17).

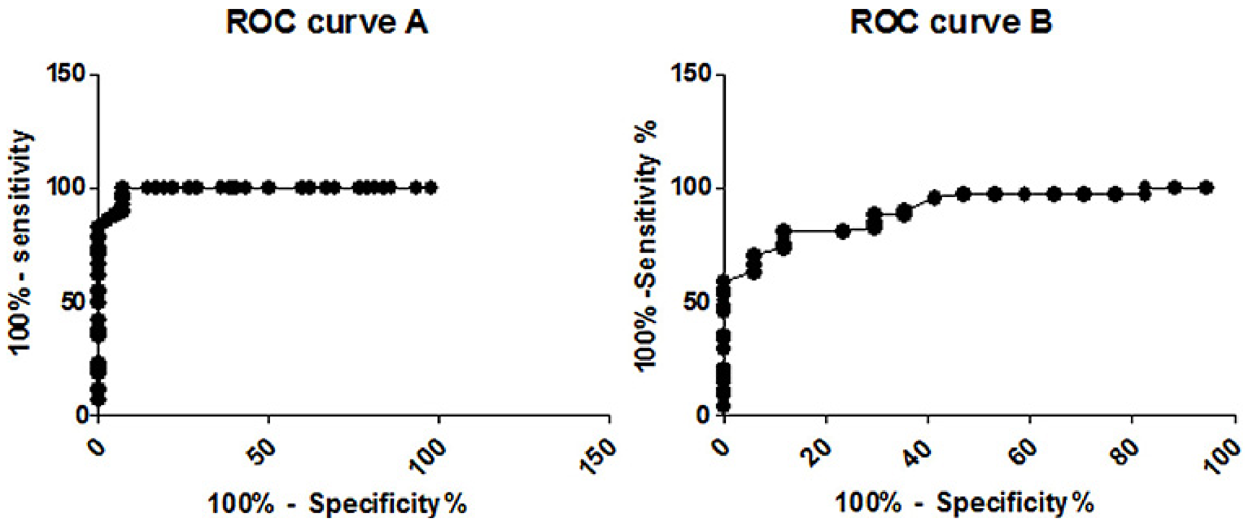

Figure 12. Receiver-operator characteristic (ROC) for chromogranin A cell density in the duodenum (A) and in the colon (B).

Prucalopride has been also been reported to decrease colonic transit time (174).

Ingested nutrients and their digestion products initiate local responses including the release of the neuroendocrine peptides/amines of the gut (see Table 1). The proteins, fat and carbohydrates content of the ingested food would influence the amount and type of the gut hormone release. These hormones regulate and control gastrointestinal motility and sensation. Thus, pre-existed abnormalities in the neuroendocrine system of the gut could be compensated for through dietary manipulation, one could compensate pre-existed abnormalities in the neuroendocrine system of the gut, and non-pharmacological approaches appears to have been proven successful (175-177).

7. CONCLUSION

IBS is a common disorder affecting 5-10% of the world's population. In addition to causing significant morbidity and reduced quality of life, it also represents an economic burden to the society. The neuroendocrine peptides/amines of the gut are likely to play a role in the pathogenesis of this disorder. These peptides/amines can be used for the diagnosis and treatment of IBS.

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Send correspondence to: Magdy El-Salhy, Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital Box 4000, 54 09 Stord, Norway, Tel: 47-53491000, Fax: 47-53491001, E-mail: magdy.el-salhy@helse-fonna.no