Endocrine cells in the oxyntic mucosa of the stomach in patients with irritable bowel syndrome

Magdy El-Salhy, Odd Helge Gilja, Doris Gundersen, Trygve Hausken

Magdy El-Salhy, Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, 5409 Stord, Norway
Magdy El-Salhy, Odd Helge Gilja, Trygve Hausken, Section for Gastroenterology, Department of Clinical Medicine, University of Bergen, 5006 Bergen, Norway
Odd Helge Gilja, National Centre for Ultrasound in Gastroenterology, Department of Medicine, Haukeland University Hospital, 5006 Bergen, Norway
Doris Gundersen, Department of Research, Helse-Fonna, 3072 Haugesund, Norway

Supported by Helse-Fonna, 3072 Haugesund, Norway

Author contributions: El-Salhy M planned the study, recruited the patients and control subjects, performed gastroscopy and morphometry, and wrote the manuscript; Gilja OH, Gundersen D and Hausken T contributed equally to the planning of the study, evaluation of the results and commented on the manuscript; all of the authors approved the submitted version of the manuscript.

Correspondence to: Magdy El-Salhy, Professor, Consultant Gastroenterologist, Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, Box 4000, 5409 Stord, Norway. magdy.el-salhy@helse-fonna.no

Telephone: +47-53-491000  Fax: +47-53-491001

Received: November 21, 2013  Revised: December 31, 2013

Accepted: February 16, 2014

Published online: May 16, 2014

Abstract

AIM: To study the different endocrine cell types in the oxyntic mucosa of patients with irritable bowel syndrome (IBS).

METHODS: Seventy-six patients with IBS were included in the study (62 females and 14 males; mean age 32 years, range 18-55 years), of which 40 also fulfilled the Rome III criteria for functional dyspepsia (FDP). Of the entire IBS cohort, 26 had diarrhea as the predominant symptom (IBS-D), 21 had a mixture of diarrhea and constipation (IBS-M), and 29 had constipation as the predominant symptom (IBS-C). Forty-three age and sex-matched healthy volunteers without any gastrointestinal complaints served as controls. The patients were asked to complete the Birmingham IBS symptom questionnaire. Both the patients and controls underwent a standard gastroscopy, during which three biopsy samples were taken from the corpus. Sections from these biopsy samples were immunostained using the avidin-biotin complex (ABC) method, for ghrelin, serotonin, somatostatin and histamine. The densities of these cell types and immunoreactivity intensities were quantified using computerized image analysis with Olympus cellSens imaging software (version 1.7).

RESULTS: The densities of the ghrelin cells in the control, IBS-total, IBS-D, IBS-M and IBS-C groups were 389 (320, 771), 359 (130, 966), 966 (529, 1154), 358 (120, 966) and 126 (0, 262) cells/mm², respectively. There was a significant difference between the tested groups (P<0.0001). Dunn’s multiple comparison test showed that the ghrelin cell density was significantly higher in IBS-D and lower in IBS-C than in the controls (P=0.03 and 0.0008, respectively). The ghrelin cell density in patients with both IBS and FDP was 489 (130, 966), and in those with IBS only 490 (130, 956). There was no statistical significant difference between these 2 groups of patients (P=0.9). The immunoreactivity intensity did not differ between any of the groups (P=0.6). The diarrhea score of the Birmingham IBS symptom questionnaire was significantly positively correlated with ghrelin cell density (r=0.65; P<0.0001) and significantly inversely correlated with that of constipation (r=0.69; P<0.0001). The densities of the serotonin cells were 63 (51, 82), 51 (25, 115), 120 (69, 128), 74 (46, 123) and 40 (0, 46) cells/mm² in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively. A statistically significant difference was found between the tested groups (P<0.0001). Posttest revealed that serotonin cell density was significantly higher in IBS-D and lower in IBS-C than in controls (P=0.02 and 0.004, respectively), but did not differ in the IBS-total and IBS-M groups from that in controls (P=0.5 and 0.4, respectively). The serotonin cell density
in patients with both IBS and FDP was 62 (25, 115) and in those with IBS only 65 (25, 123). There was no statistically significant difference between these 2 groups of patients ($P = 1$). The immunoreactivity intensity of serotonin did not differ significantly between any of the groups ($P = 0.0.9$). The serotonin cell density was significantly positively correlated with the diarrhea score of the Birmingham IBS symptom questionnaire ($r = 0.56; P < 0.0001$) and significantly inversely correlated with that of constipation ($r = 0.51; P < 0.0001$). The densities of the somatostatin cells were 97 (72, 126), 72 (0, 206), 29 (0, 80), 46 (0, 103) and 206 (194, 314) cells/mm$^2$ in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively (Figures 7 and 8). There was a statistically significant difference between the controls and the IBS subgroups ($P < 0.0001$). The density of somatostatin cells was significantly lower in the IBS-D and IBS-M groups but higher in IBS-C patients than in the controls ($P < 0.01$, $P = 0.02$, and $P = 0.0008$, respectively). The somatostatin cell density in patients with both IBS and FDP was 86 (0-194), and in those with IBS only 110 (0-206). There was no statistically significant difference between these 2 groups of patients ($P = 0.6$). There was no significant difference in somatostatin immunoreactivity intensity between the controls. The diarrhea score of the Birmingham IBS symptom questionnaire was inversely correlated with somatostatin cell density ($r = 0.38; P = 0.0007$) and was positively correlated with that of constipation ($r = 0.64; P < 0.0001$).

CONCLUSION: The finding of abnormal endocrine cells in the oxyntic mucosa shows that the endocrine cell disturbances in IBS are not restricted to the intestine. Furthermore, it appears that ghrelin, serotonin and somatostatin in the oxyntic mucosa of the stomach may play an important role in the changing stool habits in IBS through their effects on intestinal motility.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

Key words: Birmingham irritable bowel syndrome symptom questionnaire; Ghrelin; Immunohistochemistry; Serotonin; Somatostatin

Core tip: There are four endocrine cell types in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells. These cells regulate several functions that have been investigated thus far.

INTRODUCTION

The gastrointestinal endocrine cells are scattered among the mucosal epithelial cells lining the gastrointestinal lumen[1-4]. These cells can be divided into several types according to the hormone they produce. They have specialized microvilli that project into the lumen and function as sensors of the luminal contents, and respond by releasing their hormones into the lamina propria, where they act locally (paracrine mode) or via the bloodstream (endocrine mode)[5-14]. These cells interact and integrate with each other, with the enteric nervous system, and with afferent and efferent nerve fibers from the autonomic nervous system[14]. There are four types of endocrine cell in the oxyntic mucosa of the stomach: ghrelin, serotonin, somatostatin and histamine-containing (enterochromaffin-like) cells[12].

Irritable bowel syndrome (IBS) is a common disorder that affects 10%-20% of the population in the Western world, producing symptoms of abdominal pain/discomfort and altered bowel habits[6]. The findings of laboratory tests, endoscopic examinations and radiological tests are normal in these patients and the diagnosis is based mainly on symptom assessment[7]. Endocrine cell abnormalities have been reported in both the small and large intestines of IBS patients[8-29], but ghrelin cells are the only endocrine cells of the oxyntic mucosa of the stomach that have been investigated thus far[30].

The aim of this study was to determine whether there are abnormalities in the densities and immunoreactivity intensities of all of the endocrine cell types in the oxyntic mucosa of the stomach in a cohort of patients with IBS, including all IBS subtypes: those with diarrhea, constipation or a mixture of both as the predominant symptom (IBS-D, IBS-C and IBS-M, respectively).

MATERIALS AND METHODS

Patients and controls

Seventy-six patients who fulfilled the Rome III criteria for IBS were included in the study (62 females and 14 males; mean age 32 years, range 18-55 years)[30,31], of which 40 also fulfilled the Rome III criteria for functional dyspepsia (FDP). None of the patients had used proton pump inhibitor medication in the last 6 mo. Of the entire IBS cohort, 26 had IBS-D, 21 had IBS-M, and 29 had IBS-C. All of the patients underwent a complete physical examination and were investigated by way of blood tests to exclude inflammatory, liver, endocrine and any other systemic diseases. Moreover, they were submitted to a colonoscopy with segmental biopsies, which revealed the presence of a normal terminal ileum, colon and rectum in all cases.

Forty-three age and sex-matched healthy volunteers without any gastrointestinal complaints were recruited as controls via local announcements at our hospitals and in the local newspapers (32 females and 11 males; mean age 40 years, range 20-58 years).

The study was approved by the Regional Committee for Medical and Health Research Ethics West, Bergen, Norway. All subjects provided both oral and written consent to participate.

**Symptom assessment**
The patients were asked to complete the Birmingham IBS symptom questionnaire, a disease-specific tool for assessing the symptoms of patients with IBS. Its dimensions have good reliability, external validity and sensitivity. The questionnaire comprises 11 questions related to the frequencies of IBS-related symptoms. All of the questions are measured on a 5-point Likert scale. The questionnaire comprises three underlying dimensions: pain, diarrhea and constipation.

**Gastroscopy, histopathology and immunohistochemistry**
Both the patients and controls underwent a standard gastroscopy after an overnight fast, during which three biopsy samples were taken from the corpus (major curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for Helicobacter pylori (H. pylori) infection (Helicobacter pylori) and were either basket or flask-shaped, sometimes with a long basal curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for H. pylori infection between the patients and controls did not differ between the patients and controls.

The sex and age distributions did not differ significantly between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Mann-Whitney parametric test. Differences in the gender distribution and the occurrence of H. pylori infection between the patients and controls were tested using Fisher’s exact test. Differences in the age distribution were tested using the Mann-Whitney nonparametric test. Differences between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Kruskal-Wallis nonparametric test with Dunn’s posttest. Correlations were analyzed using Spearman’s nonparametric test. The data are presented as median and interquartile (25th and 75th percentile) values and differences with P < 0.05 were considered statistically significant.

**Results**

**Patients and controls**
The sex and age distributions did not differ significantly between the patients and controls (P = 0.196 and P = 0.360, respectively). The incidence of H. pylori infection did not differ between the patients (n = 3) and controls (n = 2, P = 1.0). The total score for the Birmingham IBS symptom questionnaire for the entire patient cohort (i.e., IBS-total) was 21.5 ± 0.7. The scores on the pain, diarrhea and constipation dimensions were 7.2 ± 0.4, 6.6 ± 0.4, and 7.2 ± 0.4, respectively.

**Gastroscopy, histopathology and immunohistochemistry**
The esophagus was macroscopically normal while the stomach and duodenum were both macroscopically and microscopically normal in both the patients and controls. Immunoreactive cells were found in the stomach oxyntic mucosa of both the patients and controls, and were either basket or flask-shaped, sometimes with a long basal

El-Salhy M et al. Oxyntic mucosa endocrine cells in IBS

Symptom assessment
The patients were asked to complete the Birmingham IBS symptom questionnaire, a disease-specific tool for assessing the symptoms of patients with IBS. Its dimensions have good reliability, external validity and sensitivity. The questionnaire comprises 11 questions related to the frequencies of IBS-related symptoms. All of the questions are measured on a 5-point Likert scale. The questionnaire comprises three underlying dimensions: pain, diarrhea and constipation.

Gastroscopy, histopathology and immunohistochemistry
Both the patients and controls underwent a standard gastroscopy after an overnight fast, during which three biopsy samples were taken from the corpus (major curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for Helicobacter pylori (H. pylori) infection (Helicobacter pylori) and were either basket or flask-shaped, sometimes with a long basal curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for H. pylori infection between the patients and controls did not differ between the patients and controls.

The sex and age distributions did not differ significantly between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Mann-Whitney nonparametric test. Differences in the gender distribution and the occurrence of H. pylori infection between the patients and controls were tested using Fisher’s exact test. Differences in the age distribution were tested using the Mann-Whitney nonparametric test. Differences between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Kruskal-Wallis nonparametric test with Dunn’s posttest. Correlations were analyzed using Spearman’s nonparametric test. The data are presented as median and interquartile (25th and 75th percentile) values and differences with P < 0.05 were considered statistically significant.

**Results**

**Patients and controls**
The sex and age distributions did not differ significantly between the patients and controls (P = 0.196 and P = 0.360, respectively). The incidence of H. pylori infection did not differ between the patients (n = 3) and controls (n = 2, P = 1.0). The total score for the Birmingham IBS symptom questionnaire for the entire patient cohort (i.e., IBS-total) was 21.5 ± 0.7. The scores on the pain, diarrhea and constipation dimensions were 7.2 ± 0.4, 6.6 ± 0.4, and 7.2 ± 0.4, respectively.

**Gastroscopy, histopathology and immunohistochemistry**
The esophagus was macroscopically normal while the stomach and duodenum were both macroscopically and microscopically normal in both the patients and controls. Immunoreactive cells were found in the stomach oxyntic mucosa of both the patients and controls, and were either basket or flask-shaped, sometimes with a long basal

El-Salhy M et al. Oxyntic mucosa endocrine cells in IBS

Symptom assessment
The patients were asked to complete the Birmingham IBS symptom questionnaire, a disease-specific tool for assessing the symptoms of patients with IBS. Its dimensions have good reliability, external validity and sensitivity. The questionnaire comprises 11 questions related to the frequencies of IBS-related symptoms. All of the questions are measured on a 5-point Likert scale. The questionnaire comprises three underlying dimensions: pain, diarrhea and constipation.

Gastroscopy, histopathology and immunohistochemistry
Both the patients and controls underwent a standard gastroscopy after an overnight fast, during which three biopsy samples were taken from the corpus (major curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for Helicobacter pylori (H. pylori) infection (Helicobacter pylori) and were either basket or flask-shaped, sometimes with a long basal curvature) and two from the antrum. The two antral biopsy samples were used in a rapid urease test for H. pylori infection between the patients and controls did not differ between the patients and controls.

The sex and age distributions did not differ significantly between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Mann-Whitney nonparametric test. Differences in the gender distribution and the occurrence of H. pylori infection between the patients and controls were tested using Fisher’s exact test. Differences in the age distribution were tested using the Mann-Whitney nonparametric test. Differences between the control, all IBS patients combined (IBS-total), IBS-D, IBS-M and IBS-C groups were tested using the Kruskal-Wallis nonparametric test with Dunn’s posttest. Correlations were analyzed using Spearman’s nonparametric test. The data are presented as median and interquartile (25th and 75th percentile) values and differences with P < 0.05 were considered statistically significant.
The densities of the ghrelin cells in the control, IBS-total, IBS-D, IBS-M and IBS-C groups were 389 (320, 771), 359 (130, 966), 966 (529, 1154), 358 (120, 966) and 126 (0, 262) cells/mm², respectively (Figures 1 and 2). The Kruskal-Wallis test revealed a statistically significant difference between the tested groups \((P < 0.0001)\). Dunn’s multiple comparison test showed that the ghrelin cell density was significantly higher in IBS-D and lower in IBS-C than in the controls \((P = 0.03 \text{ and } 0.0008, \text{ respectively})\).

The ghrelin cell density in patients with both IBS and FDP was 489.0 ± 68.1, and in those with IBS only 490.1 ± 73.5. There was no statistically significant difference between these 2 groups of patients \((P = 0.9)\).

The immunoreactivity intensity did not differ between any of the groups, being 133 (131, 134), 131 (125, 133), 129 (125, 133), 132 (124, 134) and 130 (123, 133) a.u. in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively \((P = 0.6)\). The diarrhea score of the Birmingham IBS symptom questionnaire was significantly positively correlated with the ghrelin cell density.

**Computerized image analysis**

The results of the quantification of different endocrine cell types in the oxyntic mucosa of the stomach in IBS subtypes are given in Table 1.

**Table 1  The densities of different endocrine cell types in controls, IBS-total, IBS-D, IBS-M and IBS-C**

<table>
<thead>
<tr>
<th>Endocrine cell type</th>
<th>Controls</th>
<th>IBS-total</th>
<th>IBS-D</th>
<th>IBS-M</th>
<th>IBS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghrelin</td>
<td>389 (320, 771)</td>
<td>359 (130, 966)</td>
<td>966 (529, 1154)</td>
<td>358 (120, 966)</td>
<td>126 (0, 262)</td>
</tr>
<tr>
<td>Serotonin</td>
<td>63 (51, 82)</td>
<td>51 (25, 115)</td>
<td>120 (69, 128)</td>
<td>74 (47, 123)</td>
<td>40 (0, 46)</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>97 (72, 126)</td>
<td>72 (0, 206)</td>
<td>29 (0, 80)</td>
<td>46 (0, 103)</td>
<td>206 (194, 314)</td>
</tr>
</tbody>
</table>

Values are expressed as median and interquartile \((25\text{th} \text{ and } 75\text{th})\). \(a^*P < 0.05, \ b^*P < 0.01 \text{ and } c^*P < 0.0001 \text{ vs controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.}

**Figure 1  Ghrelin cell densities (A) and ghrelin immunoreactivity intensities (B) in the oxyntic mucosa of the stomach of controls and IBS-total, IBS-D, IBS-M and IBS-C patients. \(a^*P < 0.05, \ b^*P < 0.01 \text{ and } c^*P < 0.0001 \text{ vs controls. IBS: Irritable bowel syndrome; IBS-total: All patients with irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-M: Patients with both diarrhea and constipation; IBS-C: Patients with constipation as the predominant syndrome.}

**Figure 2  Ghrelin-immunoreactive cells in a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.**

There were insufficient histamine cells in the biopsy samples studied to allow any reliable quantification thereof.

**Computerized image analysis**

The results of the quantification of different endocrine cell types in the oxyntic mucosa of the stomach in IBS subtypes are given in Table 1.
correlated with ghrelin cell density \((r = 0.65; P < 0.0001)\) and significantly inversely correlated with that of constipation \((r = -0.69; P < 0.0001; \text{Figure 3})\).

**Serotonin:** The densities of the serotonin cells were 63 \((51, 82), 51 (25, 115), 120 (69, 128), 74 (46, 123)\) and 40 \((0, 46)\) cells/mm\(^2\) in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively. The Kruskal-Wallis test revealed a statistically significant difference between the tested groups \((P < 0.0001)\). Dunn's posttest revealed that serotonin cell density was significantly higher in IBS-D and lower in IBS-C than in controls \((P = 0.02 \text{ and } 0.004, \text{respectively}; \text{Figures 4 and 5})\), but did not differ in the IBS-total and IBS-M groups from that in controls \((P = 0.5 \text{ and } 0.4, \text{respectively})\). The serotonin cell density in patients with both IBS and FDP was 62.0 ± 6.5, and in those with IBS only 65.2 ± 9.5. There was no statistically significant difference between these 2 groups of patients \((P = 1)\). The immunoreactivity intensity of serotonin did not differ significantly between any of the groups, being 107 \((103, 110), 106 (103, 107), 120 (69, 128), 106 (103, 108)\) and 107 \((101, 110)\) a.u. in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively \((P = 0.0.9)\).

The serotonin cell density was significantly positively correlated with the diarrhea score of the Birmingham IBS symptom questionnaire \((r = 0.56; P < 0.0001)\) and significantly inversely correlated with that of constipation \((r = -0.51; P < 0.0001; \text{Figure 6})\).

**Somatostatin:** The densities of the somatostatin cells were 97 \((72, 126), 51 (25, 115), 120 (69, 128), 74 (46, 123)\) and 40 \((0, 46)\) cells/mm\(^2\) in the control, IBS-total, IBS-D, IBS-M and IBS-C groups, respectively (Figures 7 and 8). The Kruskal-Wallis test indicated a statistically significant difference between the controls and the IBS subgroups \((P < 0.0001)\). The density of somatostatin cells was significantly lower in the IBS-D and IBS-M groups, but higher in IBS-C patients than in the controls \((P < 0.01, P = 0.02 \text{ and } 0.0008, \text{respectively})\). The somatostatin cell density in patients with both IBS and FDP was 86.3 ± 19.3, and in those with IBS only 110.1 ± 24.1. There was no statistical significantly difference between these 2 groups.
of patients \( (P = 0.6) \). There was no significant difference in somatostatin immunoreactivity intensity between the controls \( (111; 109, 113 \text{ a.u.}) \) and the IBS-total \( (112; 111, 112 \text{ a.u.}) \), IBS-D \( (111; 109, 113 \text{ a.u.}) \), IBS-M \( (113; 110, 113 \text{ a.u.}) \), and IBS-C \( (113; 111, 113 \text{ a.u.}) \) patients \( (P = 0.9) \).

The diarrhea score of the Birmingham IBS symptom questionnaire was inversely correlated with somatostatin cell density \( (r = -0.38; \ P = 0.0007) \) and was positively correlated with that of constipation \( (r = 0.64; \ P < 0.0001; \text{ Figure 9}) \).

**DISCUSSION**

The findings of the present study show that the densities
of the three main types of endocrine cells in the oxyntic mucosa of the stomach, namely ghrelin, serotonin and somatostatin cells, are abnormal in IBS patients. However, the nature of these abnormalities differ with the IBS subtype, whereby the densities of the ghrelin and serotonin cells are high in IBS-D but low in IBS-C, and the density of somatostatin cells is low in IBS-D and IBS-M but high in IBS-C. As there is no difference in the endocrine cells densities between patients with IBS/FDP and patients with IBS only, the abnormalities seen in these cells are most probably caused by IBS. The immunoreactivity intensity of ghrelin, serotonin and somatostatin in IBS patients did not differ from that of controls. This indicates that the cellular content of these hormones in IBS patients is not affected relative to controls, which is an important finding given that the cellular content of a hormone reflects its cellular synthesis and release.

Abnormalities in the endocrine cells in both the small and large intestines have been reported in patients with IBS. In the small intestine, the duodenal cell densities of gastric inhibitory peptide (GIP), secretin, cholecystokinin (CCK) and somatostatin, and the ileal cell densities of serotonin and peptide YY (PYY) were found to be abnormal. In the large intestine, colonic serotonin and PYY, and rectal serotonin, PYY, enteroglucagon and somatostatin cell densities have all been found to be affected. Postinfectious IBS has been reported to be associated with elevated numbers of duodenal CCK cells and rectal serotonin cells, but decreased numbers of duodenal serotonin cells. The present observation of abnormal densities of gastric endocrine cells suggests that the endocrine cell disturbances occur throughout the gastrointestinal tract of patients with IBS.

The present findings that ghrelin cell density was high in IBS-D and low in IBS-C confirm the results of an earlier study involving another cohort of IBS patients. The present study also found that the ghrelin cell density was not affected in IBS-M. As well as regulating the release of growth hormone and roles in appetite and energy metabolism, ghrelin accelerates gastric and small and large intestine motility. Ghrelin cell density was found in the present study to be strongly positively correlated with the degree of diarrhea and inversely correlated with the degree of constipation. It is thus conceivable that changes in ghrelin cell density play a role in the development of diarrhea and constipation in IBS patients.

Serotonin stimulates colonic motility and accelerates transit through the small and large intestines. In the present study, the serotonin cell density was higher in

Figure 8 Somatostatin cells in the oxyntic mucosa of the stomach of a control subject (A), a patient with IBS-D (B), and a patient with IBS-C (C). IBS: Irritable bowel syndrome; IBS-D: Patients with diarrhea as the predominant syndrome; IBS-C: Patients with constipation as the predominant syndrome.

Figure 9 Correlations of somatostatin cell density with diarrhea (A) and constipation (B) scores as assessed by the Birmingham irritable bowel syndrome symptom questionnaire. IBS: Irritable bowel syndrome.
IBS-D and lower in IBS-C compared to healthy controls and unchanged in IBS-M. Moreover, the serotonin cell density was positively correlated with the degree of diarrhea and inversely correlated with the degree of constipation. Therefore, similar to ghrelin, serotonin seems to play a role in the development of both diarrhea and constipation in IBS patients.

Somatostatin inhibits intestinal contraction and gut exocrine and neuroendocrine secretion\[^{2,4}\]. In the present study, the somatostatin cell density was low in both IBS-D and IBS-M and high in IBS-C. Furthermore, the somatostatin cell density was inversely correlated with the diarrhea score and positively correlated with the constipation score (both assessed by the Birmingham IBS symptom questionnaire). It is therefore possible that changes in the somatostatin cell density also play a considerable role in the development of both diarrhea and constipation in IBS patients.

In conclusion, the results of the present study show that the endocrine cells in the oxyntic mucosa of the stomach in IBS patients are affected and thus that the endocrine cell disturbances observed in IBS are not restricted to the intestine. Furthermore, it appears from the present findings that ghrelin, serotonin and somatostatin in the oxyntic mucosa of the stomach may play an important role in the change in stool habits in IBS via their effects on intestinal motility. These observations shed light on the pathophysiology of IBS and agonists and/or antagonists to the hormones described can probably be used in the near future in the treatment of patients with IBS.

**REFERENCES**

18. El-Salhy M, Gilja OH, Gundersen D, Hatlebakk JG, Haus-
El-Salhy M et al. Oxyntic mucosa endocrine cells in IBS

ken T. Endocrine cells in the ileum of patients with irritable bowel syndrome. World J Gastroenterol 2014; 20: 2383-2391 [PMID: 24605036]


20 Coates MD, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszky H, Crowell MD, Sharkey KA, Gershon MD, Mawe GM, Moses PL. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology 2004; 126: 1657-1664 [PMID: 15198158]


26 Dunlop SP, Jenkins D, Neal KR, Spiller RC. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. Gastroenterology 2003; 125: 1651-1659 [PMID: 14724817]


33 Roalle AK, Roberts LM, Wilson S. Evaluation of the Birmingham-


57 Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. *Curr Opin Endocrinol Diabetes Obes* 2013; 20: 14-21 [PMID: 23222853 DOI: 10.1097/MED.0b013e32832b3b70] [PMID: 19885611]


P- Reviewers: Amornyotin S, Desilets DJ, Tham TCK
S- Editor: Qi Y  L- Editor: Roemmele A  E- Editor: Zhang DN