Interaction between ingested nutrients and gut endocrine cells in patients with irritable bowel syndrome (Review)

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Abstract. Several endocrine cell abnormalities have been reported in different segments of the gastrointestinal tract of patients with irritable bowel syndrome (IBS). These cells have specialized microvilli that project into the lumen; they function as sensors for the gut contents and respond to luminal stimuli (mostly ingested nutrients) by releasing hormones into the lamina propria, where they exert their effects via a paracrine/endocrine mode of action. Certain food items trigger the symptoms experienced by IBS patients, including those rich in fermentable oligo-, di- and monosaccharides, and polyols (FODMAPs). In this review, we present the argument that the effects of both FODMAPs and the proportional intake of proteins, fats and carbohydrates on IBS symptoms may be caused by an interaction with the gut endocrine cells. Since the gut hormones control and regulate gastrointestinal motility and sensation, this interaction may be responsible for abnormal gastrointestinal motility and the visceral hypersensitivity observed in these patients. There is no consistent evidence that IBS patients suffer from food allergy. The role of gluten intolerance in the development of IBS symptoms in these patients remains a matter of controversy. Individual guidance on food management, which includes restrictions in the intake of FODMAP-rich foods and testing diets with different proportions of proteins, fats and carbohydrates has been found to reduce the symptoms, improve the quality of life, and make the habitual diet of IBS patients more healthy.

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Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder with a worldwide prevalence of 10-20% (1-15). The diagnosis of IBS is based mainly on the assessment of the symptoms, which are abdominal discomfort/pain, altered bowel habits and abdominal bloating/distension (1,4). Patients with IBS can be subdivided into four subtypes according to the Rome III criteria and based on the stool pattern: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed diarrhea and constipation (IBS-M) and unclassified IBS (U-IBS) (16,17). IBS is usually diagnosed in younger patients (i.e., <50 years of age) and is more common in women than in men (3-6,8,9,11, 12,14,15,18,19). Although IBS is not known to be associated with the development of serious disease or with excess mortality, it considerably reduces the quality of life of patients (1,19-21). In addition to the increased morbidity caused by IBS, this condition represents an economic burden to society as a result of the overconsumption of healthcare resources by and low productivity of IBS patients (22).

IBS patients often associate their symptoms with specific food items, such as milk and milk products, wheat products, caffeine, certain meats, cabbage, onion, peas/beans, hot spices, fried foods and smoked foodstuffs (23-25). However, surveys of the diets of IBS patients have failed to detect any differences in diet composition between IBS patients and the community as regards the intake of energy, carbohydrates, proteins and fats (26-32). However, a study on food intolerance and IBS found that 62% of the subjects had either limited or excluded food items from their daily intake, and 12% of these subjects had made such drastic changes in their diet that nutritional deficiencies could be foreseen in the long term (33).
Certain studies have found IBS patients to be intolerant to various alcoholic beverages and generally have a low alcohol consumption (23,29). However, other studies found that the alcohol intake in patients with IBS was the same as or higher than that in the background population (30,31). The common belief among IBS patients is that lactose is the main cause of their symptoms, and consequently, they often reduce their intake of milk and milk products (29,31,34,35). Milk and other dairy products are the most important dietary source of calcium, vitamin B2 (riboflavin) and phosphorus in the Western world (36). Thus, while IBS patients consume more products that are alternatives to milk, such as soy, rice and oat milk, they have a low daily intake of calcium, vitamin B2 and phosphorus (29).

IBS patients have a lower consumption of foods known to be rich in fermentable oligo-, di- and monosaccharides, and polyols (FODMAPs), such as spaghetti, pasta, rice, millet, couscous and buns than healthy controls (29). Moreover, IBS patients have lower consumptions of certain vegetables (raw vegetables, raw broccoli, paprika, onion, leeks, garlic, cabbage, tomatoes, mushrooms and green beans) (29). On the other hand, they consume more FODMAP-rich fruits and vegetables, such as grapes, pears, peaches, peas, mango, plums and melon (29).

The importance of dietary factors and the associations between diet and symptoms in IBS have been discussed in the literature (23,37-41). The aim of this review was to shed light on the possible interaction between dietary intake and gut hormones, and the importance of diet management in reducing the symptoms and improving the quality of life of IBS patients.

2. The role of diet in IBS

The effect of diet on IBS symptoms may be attributed to the interaction between poorly absorbed carbohydrates/fiber and the intestinal bacterial flora, or between ingested nutrients and the gut neuroendocrine system, and food allergy or intolerance.

Interaction between poorly absorbed carbohydrates/fiber and the intestinal bacterial flora. Certain short-chain carbohydrates (FODMAPs) are poorly absorbed, resulting in a significant proportion of them reaching the distal small bowel and colon (42,43), where they provide a substrate for bacterial fermentation. This results in the production of gas, with the consequent distension of the large intestine and increased intraluminal pressure. FODMAPs include fructose, lactose, sugar alcohols (sorbitol, maltitol, mannitol, xylitol and isomalt), fructans and galactans. Fructose and lactose are present in low-calorie food products. Galactans and fructans are present in wheat, rye, garlic, onions, legumes, cabbage, artichokes, leeks, asparagus, lentils, inulin, soy, Brussels sprouts and broccoli (39,40,44). A low intake of FODMAPs has been found to reduce the gastrointestinal symptoms in patients with IBS (42,43,45,46).

Increasing the intake of dietary fiber is a standard recommendation for patients with IBS (47). However, in clinical practice, increased fiber intake in these patients has been shown to increase the symptoms of abdominal pain, bloating and distension. The examination of the effects of fiber intake on IBS symptoms has revealed that increased fiber intake does not improve symptoms compared with a placebo or a low-fiber diet (47). However, it has been reported that the intake of soluble fiber is effective in improving overall IBS symptoms relative to consuming insoluble fiber (47-50).

The effects of FODMAPs and fiber on IBS symptoms are strongly associated with the intestinal flora. The dominance of Clostridium spp. in the intestinal flora, which break down FODMAPs and fiber, results in gas production, with a consequent increase in the distension of the large intestine, causing abdominal discomfort or pain. Food supplements with beneficial bacteria, such as Lactobacillus spp. and Bifidobacterium spp. would result in a greater tolerance to both FODMAPs and fiber, since these bacteria do not produce gas on fermenting carbohydrates. It has been reported that the intestinal flora of IBS patients comprise fewer Lactobacillus spp. and Bifidobacterium spp. than the flora of healthy individuals (51,52).

Interaction between ingested nutrients and the gut neuroendocrine system. The gut endocrine cells are spread between the epithelial cells of the mucosa facing the gut lumen (1,53). They are present in all the segments of the gastrointestinal tract apart from the esophagus (1). There are several different populations of gut endocrine cells (22,32,53-55); the distribution, functions and modes of action of the most important types have been reported previously (22,32,53,56-68). Some of the different endocrine cell types are located only in specific areas of the gut, while others are found throughout the gut (53-55). Thus, serotonin- and somatostatin-secreting cells are found throughout the gastrointestinal tract, while those producing ghrelin and gastrin are found in the stomach; those producing secretin, cholecystokinin (CCK), gastric inhibitory peptide (GIP) and motilin are found in the upper small intestine, and those producing polypeptide YY (PYY), pancreatic polypeptide (PP) and enteroglucagon are located in the lower small intestine and large intestine (53-55). These cells have specialized microvilli that project into the lumen and function as sensors for the gut contents (mostly for nutrients), and respond to luminal stimuli by releasing their hormones into the lamina propria (Fig. 1) (69-81). The gut intraluminal contents of carbohydrates, proteins and fats triggers the release of the different signaling substances (i.e., hormones) from the gut endocrine cells (1,53). These signaling substances may exert their actions locally on nearby structures (paracrine mode) or by entering the circulating blood and reaching distant targets (endocrine mode) (82). The gut endocrine cells interact and integrate with each other, and with the enteric nervous system (ENS) and the afferent and efferent nerve fibers of the autonomic nervous system and the central nervous system (CNS) (22,53,59,83). In doing so, they regulate several functions of the gastrointestinal tract, including visceral sensation, motility, secretion, absorption, local immune defense and food intake (22,53-55,83).

Several abnormalities in the gut endocrine cells have been described in IBS patients (84-100), as summarized in Table I and illustrated in Figs. 2 and 3. The etiology of these abnormalities in sporadic (non-specific) IBS patients can be genetically inherited and/or caused by environmental factors. A genetic etiology is supported by the familial aggregation of IBS and the results of twin studies (101-111). Alternatively, endocrine cells have a rapid turnover, and it is possible that factors related
to luminal content, such as diet or bacterial flora can provoke an increase or decrease in the endocrine cell population (54,55). In post-infectious IBS (PI-IBS), the abnormalities in gut endocrine cells may be the result of endocrine/immune interactions (i.e., the endocrine/immune axis), which are in turn caused by low-grade inflammation following gastroenteritis in predisposed individuals (112,113).

As indicated in Table I, gastrointestinal hormone release is triggered by the intraluminal contents of nutrients; thus, the release of ghrelin, CCK and PYY is triggered by proteins and fat, and ghrelin release is suppressed by the presence of carbohydrates. Consequently, while a diet that is poor in fat, proteins and carbohydrates would aggravate the symptoms in patients with IBS-D, a diet containing low levels of fat and proteins and high levels of carbohydrates would worsen the symptoms in patients with IBS-C. In patients with PI-IBS, the symptoms would be worsened by food rich in proteins and fat.

In IBS patients, the gut endocrine cells may be responsible for the abdominal pain/discomfort resulting from the aforementioned gas production and consequent increase in intraluminal pressure and large-intestinal distension following the breakdown of FODMAPs and fibers by the intestinal bacterial flora. An increase in the intraluminal pressure would possibly result in the release of serotonin and substance P into the interstitial fluid. Serotonin activates the submucosal sensory branch of the ENS, which conveys the sensation to the CNS, possibly causing the sensation of abdominal pain/discomfort (114,115). Furthermore, serotonin controls gastrointestinal motility and chloride secretion via interneurons and motor neurons, which may result in disturbances in both motility and gastrointestinal secretion (114,115).

Food allergy or intolerance. There is neither consistent evidence for an allergic response nor documented evidence for intolerance to a specific food in IBS (1,116-122). Although a food allergy mediated by mucosal mechanisms has been suggested for IBS (123,124), these mechanisms may play a role in only a subset of patients who may have atopy or PI-IBS (1,123,125). Different
Table I. Summary of the abnormalities in the endocrine cell densities in different segments of the gastrointestinal tract of IBS patients, and the factors responsible for the release of gut hormones and the functions of these hormones.

| Gut segment | Endocrine cell type | Released by | Functions | IBS-D | IBS-C |
|-------------|---------------------|-------------|-----------|-------|-------|
| Stomach     | Ghrelin             | Protein and fat ingestion. Suppressed by carbohydrate ingestion. | Increases gastric and intestinal motility, and stimulates appetite and food intake. | High | Low   |
|             | Serotonin           | Adrenaline, acetylcholine, acidification, and increased intraluminal pressure. | Activates the submucosal sensory branch of the ENS, inhibits gastric emptying, stimulates colonic motility, and accelerates small- and large-intestinal transit. | Normal | High  |
|             | Gastrin             | Intraluminal peptides, amino acids, calcium, amines, low pH, and prostaglandins. Release inhibited by somatostatin. | Stimulates gastric acid secretion and histamine release, and stimulates contraction of the LES and antrum. | High | High  |
|             | Somatostatin        | Meal and acidification of the stomach. | Inhibits gut exocrine and neuroendocrine secretion, and inhibits intestinal contraction. | Low  | Low   |
| Small intestine |               |             |           |       |       |
| Duodenum    | CCK                 | Intraluminal protein and fat. | Stimulates pancreatic exocrine secretion and growth, regulates food intake, inhibits gastric emptying, and stimulates gallbladder contraction and intestinal motility. | Low | Normal |
|             | Secretin            | Acidification of the intestinal contents. | Stimulates pancreatic bicarbonate and fluid secretion; inhibits gastric emptying; inhibits contractile activity of the small and large intestines. | Low | Normal |
| Ileum       | GIP                 | Intraluminal glucose; amino acids and fat. | Inhibits gastric acid secretion. | Low | Low   |
|             | Somatostatin        | Intraluminal glucose; amino acids and fat. | Inhibits gastric acid secretion. | Low | Low   |
| Large intestine |             |             |           |       |       |
| Colon       | Serotonin           | Intraluminal glucose; amino acids and fat. | Inhibits gastric acid secretion. | Low | Low   |
|             | PYY                 | Protein- and fat-rich meals. | Delays gastric emptying, stimulates the absorption of water and electrolytes; major mediator of the ileal brake. | Normal | High  |
|             |                     |             |           |       |       |
|             |                     |             |           |       |       |
|             |                     |             |           |       |       |
classes of antibodies (IgG) have been implicated in food-related allergies in IBS (126, 127). The results of studies on this subject are controversial, possibly since the tests used are not sufficiently sensitive or specific (31,116,117,123,124,128-133).

The association between IBS and celiac disease (CD) has drawn much attention of late. The breadth of the spectrum of symptoms in IBS means that there is the potential for overlap with CD symptomatologies. Thus, patients with CD presenting with relatively vague abdominal symptoms can be diagnosed as having IBS (39,40). Furthermore, the symptoms of both IBS and CD patients are triggered by the ingestion of wheat products. The reported prevalence of CD in IBS varies between 0.04 and 4.7% (134-144). It has been suggested that IBS patients with wheat intolerance and who carry the genotype associated with CD (HLA DQ2 or DR3), but do not have typical serological markers or changes in small-intestine histology exhibit other immunological evidence of gluten reactivity and response to a gluten-free diet. Although this has been dismissed by clinicians as a placebo effect, there is emerging new data regarding non-celiac gluten sensitivity (147). The existence of non-celiac gluten intolerance has been demonstrated by a double-blinded, randomized, placebo-controlled rechallenge trial (148). However, the diets of the subjects in that study excluded wheat products, which contain gluten, as well as fructans and galactans. A recent placebo-controlled, cross-over study found no evidence of the specific effects of gluten in non-celiac gluten sensitivity (149). Thus, the role of gluten intolerance in IBS has yet to be clarified, and further studies are required.

### 3. Diet management in IBS

It is clear that IBS patients need guidance on diet management. Providing IBS patients with diet guidance has been found to reduce symptoms and to improve their quality of life (29,150). Furthermore, this guidance leads IBS patients to consume a more adequate diet in terms of the levels of vitamins and minerals, and makes them aware of all FODMAP-rich foods, the consumption of which they should either avoid or reduce. They also consume foods supplemented with *Lactobacillus* spp.

| Gut segment | Endocrine cell type | Released by | Functions | IBS-D | IBS-C |
|-------------|---------------------|-------------|-----------|-------|-------|
| Rectum      | PYY                 | Protein- and fat-rich meals. | Delays gastric emptying, stimulates the absorption of water and electrolytes; major mediator of the ileal brake. | Low | Low |
| Enteroglucagon | Intraluminal carbohydrates and fat. | Inhibits gastric and pancreatic secretion, reduces gastric motility, and has also some incretin effect. | Low | Low |
| Somatostatin | Protein- and fat-rich meals. | Delays gastric emptying, stimulates the absorption of water and electrolytes; major mediator of the ileal brake. | High | High |

IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-C, constipation-predominant IBS; LES, lower esophageal sphincter; GIP, gastric inhibitory peptide.
and *Bifidobacterium* spp., which increase their tolerance to FODMAPs (29).

Diet guidance should be individualized, since IBS patients have different tolerances to various FODMAP-rich foods, possibly due to differences in their intestinal flora. The aim of diet guidance should be to provide information about FODMAPs and their role in the symptoms of individual patients, and to instruct them to avoid such foods. Moreover, the effects of the proportional intakes of protein, fats and carbohydrates on their symptoms should be examined. In clinical practice, we have found that reducing the carbohydrate or fat intake and increasing the protein intake improves the symptoms in certain patients. In addition, IBS patients should be encouraged to consume foods that are supplemented with *Lactobacillus* spp. and *Bifidobacterium* spp. Other lifestyle factors, such as regular exercise and regular intake of probiotics, may augment the effect of diet management (151).

4. Conclusion

Diet triggers symptoms in IBS patients, possibly as a result of interactions with the gut endocrine cells, which are defective in IBS patients. The effects of the food content of FODMAPs and fiber on IBS symptoms are possibly mediated through gut endocrine cells. FODMAPs in the diet increase the osmotic pressure and provide a substrate for bacteria fermentation and gas production in the large intestine, resulting in abdominal distension. The increase in intestinal pressure may cause the release of serotonin and substance P, which in turn may result in the sensation of abdominal discomfort or pain. The protein, fat and carbohydrate content of ingested foods determine the amount and type of gut hormones released, which will in turn regulate and control gastrointestinal motility and sensation, that have been reported to be abnormal in IBS patients (152-179). Although it is possible that IBS patients suffer from gluten intolerance, further studies are required to confirm this before any definitive conclusions can be drawn. Guidance on diet management, including individually tailored restrictions of FODMAP-rich foods and the testing of protein-, fat- and carbohydrate-rich/poor diets reduce IBS symptoms and accordingly improve the overall management of the health of IBS patients.

References

1. El-Salhy M, Gundersen D, Hatlebakk JG and Hausken T: Irritable bowel syndrome: diagnosis, pathogenesis and treatment options. Nova Science Publishers, Inc., New York, 2012.
2. Thompson WG: A world view of IBS. In: Irritable Bowel Syndrome. Camilleri M and Spiller RC (eds). Saunders, Philadelphia and London, pp17-26, 2002.
3. Agreus L, Svardbudd K, Nyren O and Tibblin G: Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. Gastroenterology 109: 671-680, 1995.
4. Thompson WG, Irvine EJ, Pare P, Ferrazzi S and Rance L: Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. Dig Dis Sci 47: 225-235, 2002.
5. Kennedy TM, Jones RH, Hungin AP, Johansen J and Madsen J: The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 17: 643-650, 2003.
6. Jones R and Lydeard S: Irritable bowel syndrome in the general population. BMJ 304: 87-90, 1992.
7. Bordie AK: Functional disorders of the colon. J Indian Med Assoc 58: 451-456, 1972.
8. O’Keefe JA, El-Salhy M, Zinsmeister AR, Scientific Advisory Board and the Rome II Task Force: Guidelines on the irritable bowel syndrome: mechanisms and practical management. J Clin Gastroenterol 38: 558-560, 2004.
9. Williams EA, Nai X and Corfe BM: Dietary intakes in people with irritable bowel syndrome compared with the general population. BMC Gastroenterol 11: 9, 2011.
10. Jarrett M, Heitkemper MM, Bond EF and Georges J: Comparison of diet composition in women with and without functional bowel disorder. Gastroenterol Nurs 16: 253-258, 1994.
11. Saito YA, Locke GR III, Weaver AL, Zinsmeister AR and Talley NJ: Diet and functional gastrointestinal disorders: a population-based case-control study. Am J Gastroenterol 100: 2743-2748, 2005.
12. Williams EA, Nai X and Corfe BM: Dietary intake in people with irritable bowel syndrome. BMC Gastroenterol 11: 9, 2011.
13. Ostgaard H, Hausken T, Gundersen D and El-Salhy M: Diet and effects of diet management on quality of life and symptoms in patients with irritable bowel syndrome. Mol Med Rep 5: 1382-1390, 2012.
14. Bohn L, Storsrud S, Tornblom H, Bengtsson U and Simren M: Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. Am J Gastroenterol 108: 634-641, 2013.
15. Jarrett M, Heitkemper MM, Bond EF and Georges J: Comparison of diet composition in women with and without functional bowel disorder. Gastroenterol Nurs 16: 253-258, 1994.
16. Saito YA, Locke GR III, Weaver AL, Zinsmeister AR and Talley NJ: Diet and functional gastrointestinal disorders: a population-based case-control study. Am J Gastroenterol 100: 2743-2748, 2005.
17. Williams EA, Nai X and Corfe BM: Dietary intakes in people with irritable bowel syndrome. BMC Gastroenterol 11: 9, 2011.
18. Ostgaard H, Hausken T, Gundersen D and El-Salhy M: Diet and effects of diet management on quality of life and symptoms in patients with irritable bowel syndrome. Mol Med Rep 5: 1382-1390, 2012.
33. Dizdar V, Spiller R, Singh G, et al: Relative importance of abnormalities of CCK and 5-HT (serotonin) in Giardia-induced post-infectious irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 31: 853-891, 2010.

34. Monsbakken KW, Vandvik PO and Farup PG: Perceived food intolerance in subjects with irritable bowel syndrome - etiology, prevalence and consequences. Eur J Clin Nutr 60: 667-672, 2006.

35. Vesa TH, Seppo LM, Marteau PR, Sahi T and Korpela R: Role of irritable bowel syndrome in subjective lactose intolerance. Am J Clin Nutr 67: 710-715, 1998.

36. Geissler C: Human Nutrition, Geissler C and Powers H (eds). Elsevier, Churchill Livingstone, 2005.

37. Wald A and Rakel D: Behavioral and complementary approaches for the treatment of irritable bowel syndrome. Nutr Clin Pract 23: 192-201, 2008.

38. Heizer WD, Southern S and McGovern S: The role of diet in irritable bowel syndrome: a narrative review. J Am Diet Assoc 109: 1204-1214, 2009.

39. Morcos A, Dinan T and Quigley EM: Irritable bowel syndrome: role of food in pathogenesis and management. J Dig Dis 10: 237-246, 2009.

40. Eswaran S, Tack J and Chey WD: Food: the forgotten factor in the irritable bowel syndrome. Gastroenterol Clin North Am 40: 141-162, 2011.

41. Austin GL, Dalton CB, Hu Y, et al: A very low-carbohydrate diet improves symptoms and quality of life in diarrhea-predominant irritable bowel syndrome. Clin Gastroenterol Hepatol 7: 706-708 e701, 2009.

42. Barrett JS and Gibson PR: Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and nonconventional food intolerances: FODMAPs or food chemicals? Therap Adv Gastroenterol 5: 261-268, 2012.

43. Barrett JS: Extending our knowledge of fermentable, short-chain carbohydrates for managing gastrointestinal symptoms. Nutr Clin Pract 28: 300-306, 2013.

44. Biesiekierski JR, Rosella O, Rose R, et al: Quantification of fructans, galacto-oligosaccharides and other short-chain carbohydrates in processed grains and cereals. J Hum Nutr Diet 24: 154-176, 2011.

45. de Roest RH, Dobbs BR, Chapman BA, et al: The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. Int J Clin Pract 67: 895-903, 2013.

46. Staudacher HM, Whelan K, Irving PM and Lomer MC: Comparison of symptom response following advice for a diet low in fermentable carbohydrates (FODMAPs) versus standard dietary advice in patients with irritable bowel syndrome. J Hum Nutr Diet 24: 487-495, 2011.

47. Bijkjerck CJ, Murts JW, Knottnerus JA, Hausken T: Irritable bowel syndrome: the role of gut neuroendocrine neoplasia. Tumour Biol 31: 373-380, 2010.

48. Heizer WD, Southern S and McGovern S: The role of diet in irritable bowel syndrome. J Hum Nutr Diet 24: 141-162, 2011.

49. Ford AC, Talley NJ, Spiegel BM, et al: Soluble or insoluble fibre in irritable bowel syndrome: a randomized, controlled trial. Diabetes 54: 2390-2395, 2005.

50. Camilleri M: Peripheral mechanisms in irritable bowel syndrome. N Engl J Med 367: 1626-1635, 2012.

51. Sandstrom O and El-Salhy M: Ageing and endocrine cells of the intestinal tract. Curr Opin Endocrinol Diabetes Obes 20: 14-21, 2013.

52. Si JM, Yu YC, Fan YJ and Chen SJ: Intestinal microecology dysbalance and disorders (Review). Int J Mol Med 31: 275-282, 2013.

53. El-Salhy M, Mazzawi T, Gundersen D, Hatlebakk JG and Hausken T: The role of peptide YY in gastrointestinal diseases (Review). Eur J Endocrinol 166: G457-G461, 2007.

54. Dubrasquet M, Bataille D and Gespach C: Oxyntomodulin (glucagon-37 or bioactive enteroglucagon): a potent inhibitor of pentagastrin-stimulated acid secretion in rats. Biosci Rep 2: 391-395, 1982.

55. May CL and Kaestner KH: Gut endocrine cell development. Mol Endocrinol 23: 70-75, 2010.

56. Wad PR, Chen J, Jaffe B, Kassem IS, Blakely RD and Gershon MD: Localization and function of a 5-HT transporter in crypt epithelia of the gastrointestinal tract. J Neurosci 16: 2352-2364, 1996.

57. Gershon MD and Tack J: The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 132: 397-414, 2007.

58. Gershon MD: 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes 20: 14-21, 2013.

59. Gershon MD: Serotonin is a sword and a shield of the bowel: serotonin plays offense and defense. Trans Am Clin Climatol Assoc 123: 268-280, 2012.

60. El-Salhy M, Mazzawi T, Gundersen D, Hatlebakk JG and Hausken T: The role of peptide YY in gastrointestinal diseases (Review). Eur J Endocrinol 166: G457-G461, 2007.

61. El-Salhy M, Mazzawi T, Gundersen D, Hatlebakk JG and Hausken T: The role of peptide YY in gastrointestinal diseases (Review). Eur J Endocrinol 166: G457-G461, 2007.

62. Dakin CL, Small CJ, Batterham RL, et al: Peripheral oxyntomodulin reduces food intake and body weight gain in rats. Endocrinology 145: 2687-2695, 2004.

63. Wynne K, Park AJ, Small CJ, et al: Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. Diabetes 54: 2390-2395, 2005.

64. Camilleri M: Peripheral mechanisms in irritable bowel syndrome. N Engl J Med 367: 1626-1635, 2012.

65. Sandstrom O and El-Salhy M: Ageing and endocrine cells of the human duodenum. Mech Ageing Dev 108: 39-48, 1999.

66. Wynne K, Park AJ, Small CJ, et al: Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. Diabetes 54: 2390-2395, 2005.

67. Wolhurst G, Reimann F and Gribble FM: Intestinal sensing of nutrients. Handb Exp Pharmacol 205: 1-35, 2012.

68. Lee J, Cummings BP, Martin E, et al: Glucose sensing by gut endocrine cells and activation of the vagalfferent pathway is impaired in a rodent model of type 2 diabetes mellitus. Am J Physiol Regul Integr Comp Physiol 302: R657-R666, 2012.

69. Dapuns K, Fossmark F, Svyens H, Hauss O and Waldum HL: A meal test improves the specificity of chromogranin A as a marker of neuroendocrine neoplasia. Tumour Biol 31: 373-380, 2010.

70. Webster CL, El-Salhy M and Hausken T: Endocrine cell recognition of luminal nutrients. Am J Physiol Gastrointest Liver Physiol 292: G362-G374, 2007.

71. Hellstrom PM: Release of regulatory gut peptides somatostatin, gastrin, secretin and glucagon-like peptides derived from chromogranin and secretogranin family, new actors of innate immunity. Regul Pept 165: 102-110, 2010.
Decreased expression of serotonin transporter immunoreactivity intensity in the ileum of patients with irritable bowel disease. Mol Med Rep 9: 180-184, 2014.

El-Salhy M, Wendelbo H and Gundersen D: Low densities of serotonin and peptide YY cells in patients with irritable bowel syndrome. Dig Dis Sci 57: 1223-1225, 2012.

El-Salhy M, Lomholt-Beck B and Hausken T: Chromogranin A cell density in the ileum of patients with irritable bowel syndrome. Mol Med Rep 6: 703-709, 2007.

El-Salhy M, Hatlebakk JG, Gundersen D and Hausken T: Gastric antral endocrine cells in patients with irritable bowel syndrome. Dig Dis Sci 54: 3058-3051, 2010.

El-Salhy M, Moritz T, Gundersen D, Hongo M, Kano M and Talley NJ: Chromogranin A cell density in the ileum of patients with irritable bowel syndrome. Mol Med Rep 7: 1241-1244, 2013.

El-Salhy M, Vaali K, Dizdar V and Hausken T: Abnormal small-intestinal endocrine cells in patients with irritable bowel syndrome. Dig Dis Sci 55: 873-878, 2012.

El-Salhy M, Gundersen D, Ostgaard H, Lomholt-Beck B, Hatlebakk JG and Hausken T: Low densities of serotonin and peptide YY cells in the colon of patients with irritable bowel syndrome. Dig Dis Sci 57: 873-878, 2012.

El-Salhy M, Gundersen D, Hatlebakk JG, Lillebo E, Reinemo A and Salmelid L: Ghrelin in patients with irritable bowel syndrome. Int J Mol Med 23: 703-707, 2009.

El-Salhy M, Gilja OH, Hatlebakk JG and Hausken T: Gastric endocrine cells in the oxyntic mucosa of patients with irritable bowel syndrome. Dig Dis Sci 57: 3154-3159, 2012.

El-Salhy M, Gundersen D, Hatlebakk JG and Hausken T: Gastric antral endocrine cells in patients with irritable bowel syndrome. BMC Gastroenterol, 2013.

El-Salhy M, Gilja OH and Hausken T: Chromogranin A cell density in the stomach of patients with sporadic irritable bowel syndrome. Histol Histopathol, 2013.

El-Salhy M, Gilja OH, Hatlebakk JG and Hausken T: Gastric antral endocrine cells in patients with irritable bowel syndrome. BMC Gastroenterol, 2013.

El-Salhy M, Gilja OH and Hausken T: Chromogranin A cell density in the ileum of patients with irritable bowel syndrome. J Gastroenterol 45: 1435-1439, 2010.

El-Salhy M, Lillebo E, Reinemo A and Salmelid L: Ghrelin in patients with irritable bowel syndrome. Int J Mol Med 23: 1046-1053, 2009.
A primary care—Non-celiac wheat detection of
155. Whitehead WE and Palsson OS: Is rectal pain sensitivity a
154. Mertz H, Naliboff B, Munakata J, Niazi N and Mayer EA:
153. Ritchie J: Pain from distension of the pelvic colon by inflating
148. Newnham ED: Does gluten cause gastrointestinal symptoms
147. Aziz I and Sanders DS: Emerging concepts: from coeliac disease
145. Wahnschaffe U, Schulzke JD, Zeitz M and Ullrich R: Predictors
144. Verdu EF, Armstrong D and Murray JA: Between celiac disease
141. Shahbazkhani B, Forootan M, Merat S,
140. Hin H, Bird G, Fisher P, Mahy N and Jewell D: Coeliac disease
138. van der Wouden EJ, Nelis GF and Vecht J: Screening for coeliac

371
155. Whitehead WE and Palsson OS: Is rectal pain sensitivity a
154. Mertz H, Naliboff B, Munakata J, Niazi N and Mayer EA:
153. Ritchie J: Pain from distension of the pelvic colon by inflating
148. Newnham ED:Does gluten cause gastrointestinal symptoms
147. Aziz I and Sanders DS: Emerging concepts: from coeliac disease
145. Wahnschaffe U, Schulzke JD, Zeitz M and Ullrich R: Predictors
144. Verdu EF, Armstrong D and Murray JA: Between celiac disease
141. Shahbazkhani B, Forootan M, Merat S,
140. Hin H, Bird G, Fisher P, Mahy N and Jewell D: Coeliac disease
138. van der Wouden EJ, Nelis GF and Vecht J: Screening for coeliac

1998.
1113-1123, 2007.
1263-1271, 1999.
107:1898-1906; quiz 1907, 2012.
105: 1718-1724, 2003.
153-167, 1999.
196.
133: 236-240, 1997.
1283-2299, 2003.
110: 2293-2299, 2003.
636-643, 1995.
154: 320-328 e523, 2013.
576-580, 2011.
254: 509-514, 2012.
114-120, 2010.
530: 1081-1085, 2002.
123: 1251-1255, 2002.
133: 1113-1123, 2007.
14: 125-132, 1997.
109: 40-52, 1995.
115: 1263-1271, 1998.
115: 1187-1192, 1990.
44-45, 1999.
126-247, 2005.
115: 264-271, 2005.
404-405, 2011.
Gastroenterol Rep 7: 264-292, 2003.
Cochrane Database Syst Rev: CD003461, 2004.
444-445, 2007.
Gastroenterology 133: 231-235, 2002.
38: 772-781, 2008.
Mol Med Rep 4: 403-405, 2011.
16: 318-164, 1979.
196.
154: 283-290, 2004.
153: 364-371, 2004.
14: 275-274, 1995.
339: 16: 283-289, 2002.
20: 279-295, 1991.
34: 1607-1613, 1995.
56: 444-445, 2007.
Med Rep 8: 845-852, 2013.
105: 403-413, 2007.
104: 1879-1954, 2009.
Clin Gastroenterol Hepatol 5: 844-850; quiz 769, 2007.
Gastroenterol Clin North Am 20: 279-295, 1991.
J Intern Med 21: 389-392, 2010.
Clin Proc 79: 482-2004.
Gastroenterology 102: 1454-1460, 2007.
Arch Intern Med 163: 286-292, 2003.

34: 363-371, 2014