The role of diet in the pathogenesis and management of irritable bowel syndrome (Review)

M. EL-SALHY[1,2], H. ØSTGAARD[1,2], D. GUNDERSEN[3], J.G. HATLEBAKK[2] and T. HAUSKEN[2]

[1]Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, Stord; [2]Section for Gastroenterology, Institute of Medicine, Bergen University, Bergen; [3]Department of Research, Helse-Fonna, Haugesund, Norway

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Abstract. Most patients with irritable bowel syndrome (IBS) believe that diet plays a significant role in inducing IBS symptoms and desire to know what foods to avoid. It has been found that the intake of calories, carbohydrates, proteins and fat by IBS patients does not differ from that of the background population. IBS patients were found to avoid certain food items that are rich in fermentable oligo-, di- and monosacharides and polyols (FODMAPs), but they did have a high consumption of many other FODMAP-rich food items. The diet of IBS patients was found to consist of a low calcium, magnesium, phosphorus, vitamin B2 and vitamin A content. There is no consistent evidence that IBS patients suffer from food allergy, nor is there documented evidence that food intolerance plays a role in IBS symptoms. Abnormalities in gut hormones have been reported in IBS patients. As gut hormones control and regulate gastrointestinal motility and sensation, this may explain the abnormal gastrointestinal motility and visceral hypersensitivity reported in these patients. Guidance concerning food management which includes individually based restrictions of FODMAP-rich food items and individual evaluation of the effects of protein-, fat- and carbohydrate-rich/poor diets may reduce IBS symptoms.

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Correspondence to: Professor Magdy El-Salhy, Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, Box 4000, 54 09 Stord, Norway
E-mail: magdy.el-salhy@helse-fonna.no

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1. Introduction

Irritable bowel syndrome (IBS) is a chronic condition characterized by abdominal discomfort or pain, altered bowel habits, and often bloating and abdominal distension. The degree of symptoms varies in different patients from tolerable to severe, interfering with daily activity (1). Estimates of the prevalence of IBS vary from 12 to 30%, but using recent diagnostic criteria, it appears to affect 5 to 10% of the population worldwide (2-14). IBS is more common in women than in men and more commonly diagnosed in patients younger than 50 years of age (2-14).

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 (15-18). In an international survey of patients with IBS, patients reported an impaired health status, restriction of an average of 73 days of activity yearly, a poor health-related quality of life particularly with dietary restrictions, mood disturbances and interference with daily activity. Furthermore, this survey found that IBS patients would sacrifice 25% of their remaining life (average 15 years) and 14% would risk a 1/1,000 chance of death to receive treatment that would make them symptom-free (19).

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 visits, and 28% of referrals to gastroenterologists are IBS patients, making this a more common reason for a visit to the physician than diabetes, hypertension or asthma (20-22). Not only do IBS patients visit physicians more frequently, but they also undergo more diagnostic tests, consume more medications, miss more workdays, have low work productivity, are hospitalized more frequently and consume more overall direct costs than those without IBS (14). The annual costs (both direct and indirect) to manage patients with IBS are estimated at 15-30 billion US dollars (6,23,24).

Conventional therapy of IBS has focused on systematic relief of symptoms such as pain, diarrhoea and constipation. Evidence of the long-term benefit of pharmacological agents has been sparse, and new agents which have proven to be affective have raised issues concerning safety (25,26). Not surprisingly, other alternative therapies have been considered. Thus, cognitive behaviour therapy and gut-directed hypnotherapy have been used with good results (25).

The importance of dietary factors in IBS is controversial (26-30). Detailed studies of the relationships between diet and symptoms in IBS are surprisingly few. This represents a glaring gap that needs to be rectified. Thus, the present review was undertaken to elucidate the role of diet in the pathogenesis of IBS and the importance of using dietary factors in the treatment management of these patients.

2. Diet in IBS patients

Most patients with IBS believe diet plays a significant role in their symptoms and 63% desire to know what foods to avoid (28-31). More than 60% of IBS patients report worsening of symptoms following food ingestion; 28% within 15 min after eating and 93% within 3 h (32). Many IBS patients report problems with specific foods, most commonly implicating milk and milk products, wheat products, caffeine, certain meat, cabbage, onion, peas/beans, hot spices, fried food and smoked products as the offending foods (32,33).

One would expect, therefore, that IBS patients would be selective in their choice of food. Dietary surveys among IBS patients in the community failed, however, to detect any differences in the dietary intake between IBS patients and community controls (34-36). However, a Norwegian study on food intolerance and IBS showed that 62% of subjects had limited or excluded food items from their daily intake, and 12% of subjects had made changes in their diet so drastically that nutritional deficiencies were possible in the long run (37).

IBS patients have been found to have a lower alcohol consumption (32,37,38). They reported intolerance to various alcoholic beverages, and as many as 12% either limit or avoid such beverages (32,37).

The common believe among IBS patients is that lactose is the main cause of their symptoms (39). They have a lower consumption of milk and milk products (38). Milk and other dairy products are the most important dietary source of calcium, vitamin B2 (riboflavin) and phosphorus in the Western world, and the calcium, vitamin B2 and phosphorus content of these food items can contribute to 50-75, 30 and 20-30%, respectively of the daily dietary intake (32,37,40). IBS patients had, however, a much higher consumption of alternative milk products such as soy, rice and oat milk (38). But despite such replacement, IBS patients were found to have a low intake of calcium, vitamin B2 and phosphorus (38).

IBS patients reported a lower consumption of spaghetti, pasta, rice, millet, couscous and buns than controls. Spaghetti, pasta and couscous are products made using durum wheat which tend to be high in fermentable oligo-, di- and monosacharides and polyols (FODMAPs), while rice tends to be low (37,38,41). Furthermore, IBS patients reported a lower consumption of certain vegetables (raw vegetables, raw broccoli, paprika, onion, leeks, garlic, cabbage, tomatoes, mushrooms and green beans) (38). This is most likely the reason for the significantly lower intake of retinol equivalent, β-carotene and magnesium observed in these patients (38). On the other hand, IBS patients have a higher consumption of grapes, pears, peach, peas, mango, plums and melon (38). These are all fruits and vegetables that are rich in FODMAPs and are documented as causal symptom factors.

In conclusion, the intake of calories, carbohydrates, proteins and fat by IBS patients does not differ from the background population (38). IBS patients tend to avoid certain food items that are rich in FODMAPs, but also have a high consumption of many other FODMAP-rich food items. The diet which is consumed by IBS patients has a low calcium, magnesium, phosphorus, vitamin B2 and vitamin A content (38).

3. The role of diet in the pathogenesis of IBS

Food allergy or intolerance. Food allergies exist in 6-8% of children and 1-4% of adults (42). The term food allergy is used when a clear allergic response to a specific food has been identified such as peanuts and fish. Characteristically, a food allergy reaction occurs rapidly and is manifested as swelling, itching, hives, wheezing, nausea, vomiting, diarrhoea, abdominal pain, and/or collapse usually within less than 2 h after ingesting the offending food. This reaction is mediated by immunoglobulin E (IgE). There is no consistent evidence for a role of this type of allergic response in IBS (43-48).

Slow onset of food allergy can be mediated by mucosal mechanisms in IBS. This would involve IgE, T-lymphocytes, eosinophils, mast cells and other mucosal cells. The symptoms caused by this reaction develop days after ingestion of the offending food. This possibility is supported by reports of an abnormal increase in mucosal eosinophils and mast cells in IBS (49,50). However, these mechanisms may be the cause of IBS symptoms in only a subset of patients some of whom have atopy (51,52).

A new theory proposes that a different antibody class (IgG) may be implicated in food-related allergies in IBS (53-55). This concept, however, seems to be unclear and controversial (49,56-58). The tests used to support this concept are not sensitive or specific enough for clinical use or have not been applied (48,54,58-64).

The relationship between IBS and celiac disease (CD), one of the most common well-defined disorders based on an immunological response to a food constituent, has recently attracted much attention. It is difficult to clinically distinguish IBS from adult-onset CD (65-70). In patients with CD presenting in adulthood, minimal or atypical symptoms are often encountered (68,69,71). The breadth of the spectrum of symptoms associated with IBS results in a potential for an overlap of IBS and CD symptomatologies. Consequently, individuals with CD presenting with relatively vague abdominal symptoms are at risk of been dismissed as having IBS (29,30). The situation is further complicated by the fact that the abdominal symptoms of both IBS and CD patients are triggered by the ingestion of wheat products. In CD patients, this is due to gluten allergy, while in IBS, the effect is attributed to the long sugar polymer fructan in the wheat (29). The prevalence of CD in IBS varies in different studies and varies between 0.04 to 4.7% (71-82). Regardless of the number of CD patients among patients diagnosed with IBS, we believe that IBS patients should be routinely screened for CD. This is in line with current opinion in the field (30,37,83). Recently, it has been proposed that IBS patients with wheat intolerance and who possess the genotype associated with CD 8HLA DQ2 or DR3, but do have typical serological markers or changes in small intestine histology exhibit other

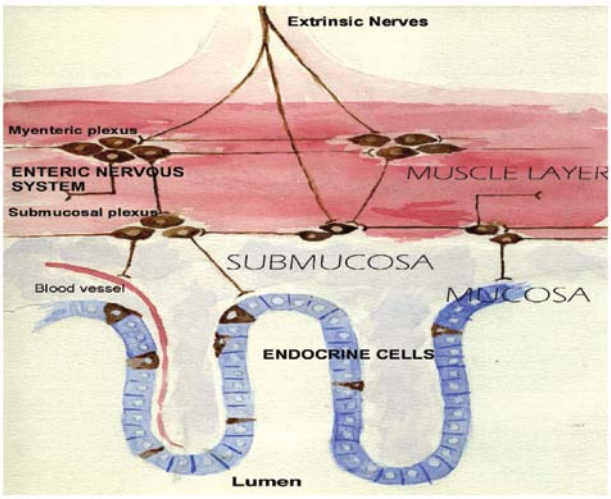

Figure 1. Schematic drawing illustrating the neuroendocrine system of the gut.

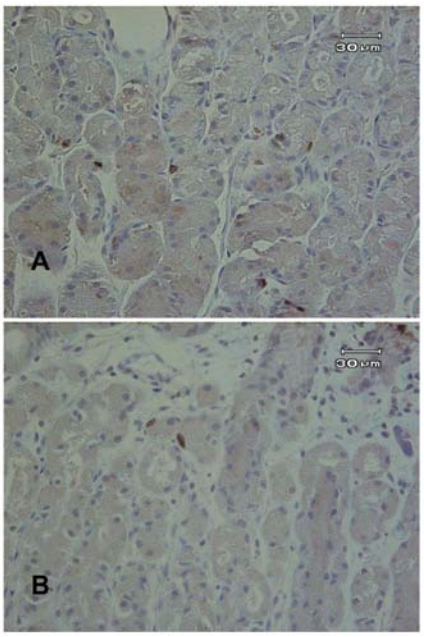

Figure 2. Ghrelin in oxyntic mucosa of a healthy subject (A) and in an IBS-C patient (B).

immunological evidence of gluten reactivity and response to a gluten-free diet (37,82).

Approximately 20-70% of IBS patients complain of subjective food intolerance (32,33,48,83-88). Food intolerances are non-toxic non-immune-mediated adverse reactions to food, including pharmacological reactions to bioactive chemicals in foods, such as histamines, sulfites, monosodium glutamate, serotonin, norepinepherine and tyramine. Furthermore, food intolerance is associated with a wide spectrum of symptoms, but these symptoms usually manifest outside the gastrointestinal tract in the form of headache, asthma and urticaria. There is no documented evidence that food intolerance plays a role in IBS symptoms.

Poorly absorbed carbohydrates and fibres. A number of short-chain carbohydrates are poorly absorbed so that a significant portion of the ingested carbohydrates enter the distal small bowel and colon. There they increase the osmotic pressure and provide a substrate for bacteria fermentation. This in turn results in gas production, distension of the large intestine with abdominal discomfort or pain. These carbohydrates are FODMAPs and include fructose, lactose, sugar alcohols (sorbitol, maltitol, mannitol, xylitol and ismalt), fructans and galactans. Fructose and lactose are present in apples, pears, watermelon, honey, fruit juices, dried fruits and milk and milk products. Polyols are used in low calorie food products. Galactans and fructans are present in such common dietary constituents as wheat, rye, garlic, onions, legumes, cabbage, artichokes, leeks, asparagus, lentils, inulin, soy, brussel sprouts and broccoli (28-30).

Fibre deficiency was widely believed to be the primary cause of IBS (89). Although increasing dietary fibres continues to be a standard recommendation for patients with IBS, clinical practice has shown that increased fibre intake in these patient increases abdominal pain, bloating and distension. Evaluation of the efficacy of fibre as a treatment for IBS has been a subject of a recent review and meta-analysis, which included 12 trials. This review revealed that patients administered fibres had persistent symptoms or no improvement in symptoms after treatment compared with a placebo or a low-fibre diet, whereas an intake of water insoluble fibres did not improve IBS symptoms. In contrast, an intake of soluble fibres has been shown to be effective in improving overall IBS symptoms (90-92).

It is noteworthy that the role of FODMAPs and fibre on IBS symptoms is associated with intestinal flora. The presence of bacteria that break down FODMAPs and fibre with gas production such as *Clostridium* spp. gives rise to distension of the large intestine with abdominal discomfort or pain. Replacing the intestinal flora with beneficial bacteria such as *Lactobacillus* spp. and *Bifidobacterium* spp. results in more tolerance to both FODMAPs and fibres. Patients with IBS have fewer *Lactobacillus* spp. and *Bifidobacterium* spp. in their intestinal flora than healthy individuals (93). These bacteria have been shown to bind to epithelial cells and inhibit pathogen binding and to enhance barrier function (94,95). Furthermore, these bacteria species do not produce gas upon fermenting carbohydrates, an effect which is amplified as they also inhibit *Clostridium* spp. (94,95). Several studies have shown an improvement in flatulence and abdominal distension with a reduction in composite IBS symptom score, following the intake of probiotics (94,95).

4. The neuroendocrine system (NES) of the gut

The NES is the gastrointestinal local regulatory system. It consists of two parts: endocrine cells scattered among the epithelial cells of the mucosa facing the gut lumen, and peptidergic and sertonergic as well as nitric oxide-containing nerves of the enteric nervous system in the gut wall (Fig. 1) (92). This system regulates several functions of the gastrointestinal tract, such as motility, secretion, absorption, microcirculation of the gut, local immune defence and cell proliferation (96-105). This regulatory system consists of a large number of bioactive messengers (Table I). These bioactive substances exert their

Table I. An overview of the most important neuroendocrine signal substances in the gut (36-39).

Signal substance	Action	Endocrine cells	Nerve fibers	Released by
Pancreatic polypeptide (PP)	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)	Inhibits pancreatic and intestinal secretion; decreases gastrointestinal motility; and is a vasoconstrictor.	-	+	Protein-rich meals.
Peptide YY (PYY)	Delays gastric emptying; inhibits gastric and pancreatic secretion; and is a major ileal brake mediator.	+	-	Protein-rich meals.
Motilin	Induces phase III MMC (migrating motor complex); stimulates gastric emptying and stimulates contraction of LES.	+	-	Protein and fat ingestion.
Ghrelin	Ghrelin increases appetite and feeding; stimulates gastric and intestinal motility.	+	-	Protein and fat ingestion and suppressed by carbohydrate ingestion.
Gastrin	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; catecole amines; low pH and prostaglandins. Somatostatin inhibits release.
Cholecyokinin (CCK)	Inhibits gastric emptying; stimulates gallbladder contraction and intestinal motility; stimulates pancreatic exocrine secretion and growth; and regulates food intake.	+	+	Intraluminal protein and fat and inhibited by somatostatin.
Secretin	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)	Incretin; and inhibits gastric acid secretion.	+	-	Intraluminal glucose; amino acids and fat.
Vasoactive polypeptide (VIP)	Stimulates gastrointestinal and pancreatic secretion; relaxes smooth muscles in the gut and causes vasodilation.	-	+	Serotonin.
Enteroglucagon	Inhibits gastric and pancreatic secretion.	+	-	Intraluminal carbohydrates and fat.
Somatostatin	Inhibits intestinal contraction; and inhibits gut exocrine and neuroendocrine secretion.	+	+	Mixed meal and acidification of the stomach.
Neurotensin	Stimulates pancreatic section; inhibits gastric secretion; delays gastric emptying; and stimulates colon motility.	+	+	Fat

Table I. Continued.

Signal substance	Action	Endocrine cells	Nerve fibers	Released by
Galanin	Inhibits gastric, pancreatic and intestinal secretion; delays gastric emptying and intestinal transit; and suppresses postprandial release of some neuroendocrine peptides.	-	+	Fat
Substance P	Stimulates smooth muscle contraction; vasodialator and inhibits gastric acid secretion.	+	+	Gut distention
Serotonin	Stimulates gastric antrum and small intestine as well as colonic motility; accelerates gastric emptying and both small intestinal and large intestinal transit.	+	+	Noradrenalin; acetylcholine; acidification and intraluminal pressure.

+, present; -, absent.

effects by an endocrine mode of action (through the circulating blood to a distant target), by a paracrine mode (by release into interstitial fluid to a nearby target), by synaptic signalling or by neuroendocrine means (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, particularly the autonomic nervous system. The signal substances of the NES may be co-localised in the same cell or may be stored separately in mono-expressed cells.

In the stomach of patients with IBS, the density of ghrelin-immunoreactive cells in the oxyntic mucosa was found to be significantly lower in IBS-constipation and significantly higher in IBS-diarrhoea patients than healthy controls (Fig. 2). Radioimmuno-assays of total or active ghrelin in tissue extracts and plasma in IBS patients did not differ from that of controls. Ghrelin plays an important role in regulating gastrointestinal motility (Table I). It has been confirmed that in order to compensate for the increase and decrease in the ghrelin cell density, the synthesis and release of ghrelin may be decreased and increased in IBS-diarrhoea and IBS-constipation patients, respectively. It has been speculated that this compensatory mechanism may be subjected from time to time to fatigue with the subsequent increased and decreased synthesis and release of ghrelin in IBS-diarrhoea and IBS-constipation with the subsequent intermittent diarrhoea or constipation noted in these patients, respectively (106).

In the small intestine, the chromogranin A-containing cell density has been found to be low in patients with IBS (Fig. 3) (107). Chromogranin A is a general marker for endocrine cells and this finding indicates that a general reduction in small intestinal endocrine cells do occur in these patients (108-110). Further studies have been carried out to determine the endocrine cell type(s) that are affected in these patients (111). The density of both cholecystokinin (CCK) and secretin cells has been found to be decreased (Fig. 4) (111). The other endocrine cell types are not affected, including serotonin cells (52). In post infectious IBS, however, the number of CCK and serotonin cells has been reported to be increased (112).

As in the small intestine, the chromogranin A cell density is low in the large intestine (107). The endocrine cell types whose densities were low include serotonin (Fig. 5) and polypeptide (PYY) cells (113). In post-infectious IBS, however, the number of serotonin and PYY cells increased (114).

Abnormal gastrointestinal motility and visceral hypersenstivity have been reported in IBS patients (115-128). It has been speculated that this abnormality is caused by genetic, psychosocial factors and stress. Gastrointestinal tract hormones play an important role in regulating gastrointestinal motility and visceral sensation (Table I). The NES of the gut in patients with IBS shows several abnormalities as mentioned previously. This points to a possible central role of the NES of the gut in the pathogenesis of IBS.

5. Diet management in IBS

Guidance on diet management for IBS patients has been found to improve quality of life and reduce symptoms (38,129). Furthermore, this guidance enhances the awareness of IBS patients of all FODMAP-rich food items and consequently their consumption of these food is avoided or reduced considerably. IBS patients were found to consume food items supplemented with *Lactobacillus* spp. and *Bifidobacterium* spp. (38). Moreover, their diet contained a normal calcium, magnesium, phosphorus, vitamin B2 and vitamin A intake (38).

The aim of dietary counselling is to inform IBS patients in regard to FODMAPs and their role in IBS symptoms and to instruct them to avoid food items rich in FODMAPs. In addition, IBS patients are instructed to assess the effects of protein-, fat- or carbohydrate-rich/poor diets on their symptoms.

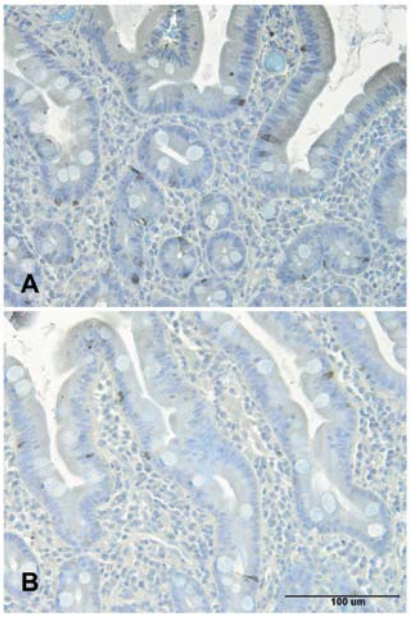

Figure 3. Chromgranin A cells in the duodenum of a healthy subject (A) and in an IBS patient (B).

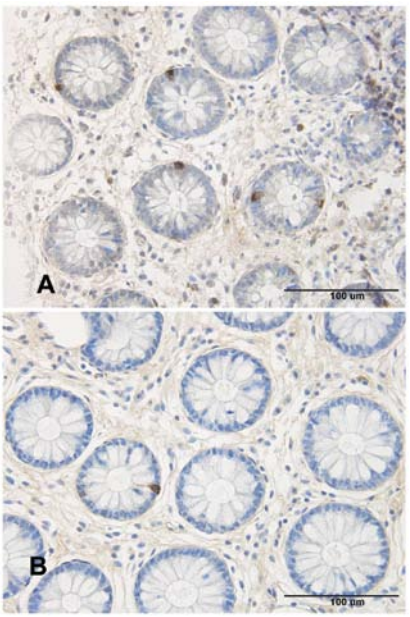

Figure 5. Serotonin cells in the colon of a healthy control (A) and in a patient with IBS (B).

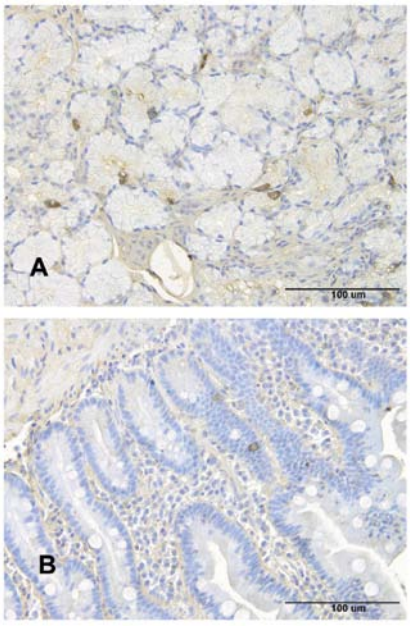

Figure 4. Cholecystokinin (CCK) cells in the duodenum of a healthy subject (A) and in a patient with IBS (B).

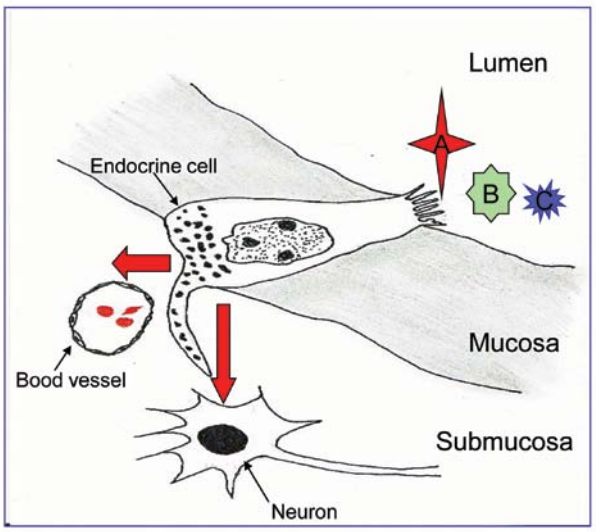

Figure 6. Schematic drawing illustrating the release of different gut hormones upon the intraluminal content of various nutrients. Depending on the intraluminal content of proteins (A), fat (B) or carbohydrates (C), a certain gut hormone is released to the interstitial fluid. It may reach the blood stream and act as a hormone, or close to a target (paracrine action) or act on a neuron in the enteric nervous system acting as a neurotransmitter/neuromodulator.

Restriction of FODMAP-rich food items should be individualized. IBS patients have different tolerance to various FODMAP-rich food items (129). This is probably due to a difference in the intestinal bacterial flora between IBS patients. In addition, IBS patients should be encouraged to consume food items supplemented with *Lactobacillus* spp. and *Bifidobacterium* spp.

The gut intraluminal content of proteins, fat or carbohydrates triggers the release of certain gut hormones (Table I and Fig. 6). IBS patients manifest abnormalities in gut hormones as mentioned previously. Through the assessment of the effects of protein-, fat- or carbohydrate-rich/poor diets on symptoms, a control of the release of certain gut hormones can be achieved. For example, IBS patients have a low density of CCK cells, and a fat-rich diet could increase the release of this hormone and likely reduce the symptoms caused by this low density. In contrast, in post-infectious IBS when a high density of CCK has been reported, a fat-poor diet would reduce CCK release. Such a response has been reported in IBS patients, where a fatty meal elicited an exaggerated and prolonged CCK release (130). In accordance with the advice concerning

FODMAPs, the assessment should be carried out individually. Clinical experience has shown that tolerance to protein, fat or carbohydrates varies considerably among IBS patients (130). This could be explained by a different abnormality in gut hormones in different IBS patients, although they may have the same symptoms. This assumption is supported by findings in patients with idiopathic slow transit constipation, considered by many as extreme IBS-C. Different abnormalities in neuroendocrine peptides have been found in different patients, although they present with the same symptoms (131).

6. Conclusion

Diet plays a major role in the symptoms of IBS patients. Symptoms are brought about by food items consisting of FODMAPs. FODMAPs increase the osmotic pressure and provide a substrate for bacterial fermentation and gas production in the large intestine. This results in symptoms such as distension of the large intestine with abdominal discomfort or pain. The protein, fat and carbohydrate content of ingested foods determines the amount and the type of the gut hormone release. These hormones regulate and control gastrointestinal motility and sensation. Abnormalities have been reported in IBS patients with the subsequent disturbance of motility and sensation.

Guidance concerning food management which includes individualized restriction of certain FODMAP-rich food items and individual assessment of the effects of protein-, fat- and carbohydrate-rich/poor diets may reduce IBS symptoms.

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