Neuropeptides 79 (2020) 101973

Contents lists available at ScienceDirect

Neuropeptides

journal homepage: www.elsevier.com/locate/npep

News and Reviews

Possible role of peptide YY (PYY) in the pathophysiology of irritable bowel syndrome (IBS)

Magdy El-Salhy[a,b,c,*], Jan Gunnar Hatlebakk[b,c], Trygve Hausken[b,c]

[a] Section for Gastroenterology, Department of Medicine, Stord Hospital, Stord, Norway
[b] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[c] National Centre for Functional Gastrointestinal Disorders, Bergen, Norway.

ARTICLE INFO

Keywords:
IBS
Motility
NPY
Secretion, stem cells
Visceral hypersensitivity

ABSTRACT

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder of unknown aetiology for which there is no effective treatment. Although IBS does not increase mortality, it reduces the quality of life and is an economic burden to both the patients themselves and society as a whole. Peptide YY (PYY) is localized in endocrine cells located in the ileum, colon and rectum. The concentration of PYY and the density of PYY cells are decreased in both the colon and rectum but unchanged in the ileum of patients with IBS. The low density of PYY cells in the large intestine may be caused by a decreased number of stem cells and their progeny toward endocrine cells. PYY regulates the intestinal motility, secretion and absorption as well as visceral sensitivity via modulating serotonin release. An abnormality in PYY may therefore contribute to the intestinal dysmotility and visceral hypersensitivity seen in IBS patients. Diet management involving consuming a low-FODMAP diet restores the density of PYY cells in the large intestine and improves abdominal symptoms in patients with IBS. This review shows that diet management appears to be a valuable tool for correcting the PYY abnormalities in the large intestine of IBS patients in the clinic.

1. Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder worldwide (El-Salhy, 2012, 2015). Moreover, about one-third of patients with ulcerative colitis and about a half of patients with Crohn's disease suffer from IBS while in remission (Ansari et al., 2008; El-Salhy et al., 2014b; El-Salhy et al., 2014d; Isgar et al., 1983; Keohane et al., 2010; Minderhoud et al., 2004; Simren et al., 2002). In addition, about one-third of patients with coeliac disease suffer from IBS symptoms despite adhering to a gluten-free diet (El-Salhy et al., 2015). The main symptoms of IBS are recurrent abdominal pain and altered bowel habits (El-Salhy, 2015). Symptoms vary in both their degree and temporal pattern between patients: from mild to severe, and from daily symptoms to being symptom-free for months (Agreus et al., 1995; Drossman et al., 1993). IBS is usually diagnosed in patients younger than 50 years (Agreus et al., 1995; Drossman et al., 1993). The aetiology of IBS is unknown and the condition lacks an effective treatment.

2. Peptide YY

Since its discovery, peptide YY (PYY) has been found in the endocrine cells that are present between the epithelial cells lining the human ileum, colon and rectum (El-Salhy et al., 1983a; Tatemoto, 1982a; Tatemoto and Mutt, 1980). PYY cells have also been found in the intestine of several vertebrates (El-Salhy, 1984; El-Salhy et al., 1981; El-Salhy et al., 1982; El-Salhy et al., 1983b).

Like other enteroendocrine cells, PYY cells have specialized sensory microvilli projecting into the intestinal lumen, and they respond to luminal stimuli such as nutrients by releasing their hormones into the lamina propria (Furness et al., 1999; Furness et al., 2013). A protein-rich meal reportedly stimulates the release of PYY (El-Salhy et al., 2016). PYY cells also possess a basal cytoplasmic process that is about 70 μm long and is believed to be involved in their paracrine mode of action (Bohorquez et al., 2011). This process has been shown to exhibit neuronal axon-like characteristics, and has been named a neuropod (Bohorquez et al., 2011; Bohorquez et al., 2014; Bohorquez et al., 2015). Enteroendocrine cells—and most probably including PYY cells—contain synaptic vesicles and synthetize presynaptic proteins such as synapsin 1, piccolo, bassoon, MUNC13B, RIMS2, latrophilin, and transsynaptic neurexin (Bohorquez et al., 2014; Bohorquez et al., 2015). These cells also synthetize transsynaptic neuroligins 2 and 3, homer 3, and postsynaptic density 95 (Bohorquez

* Corresponding author at: Section for Gastroenterology, Department of Medicine, Stord Helse-Fonna Hospital, Box 4000, 54 09, Stord, Norway.
E-mail addresses: Magdy.el-salhy@helse-fonna.no (M. El-Salhy), Jan.gunnar.hatlebakk@helse-bergen.no (J.G. Hatlebakk), Trygve.hausken@helse-bergen.no (T. Hausken).

https://doi.org/10.1016/j.npep.2019.101973
Received 7 June 2019; Received in revised form 15 August 2019; Accepted 18 September 2019
Available online 24 October 2019

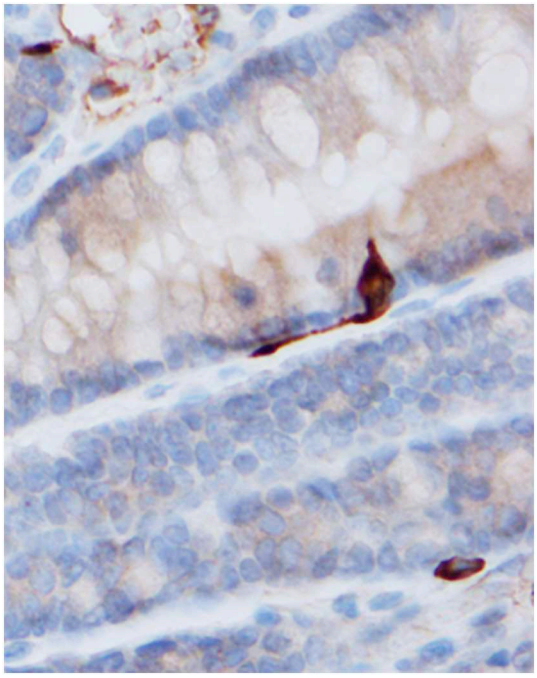

Fig. 1. An intestinal PYY cell with a long basal cytoplasmic process (neuropod).

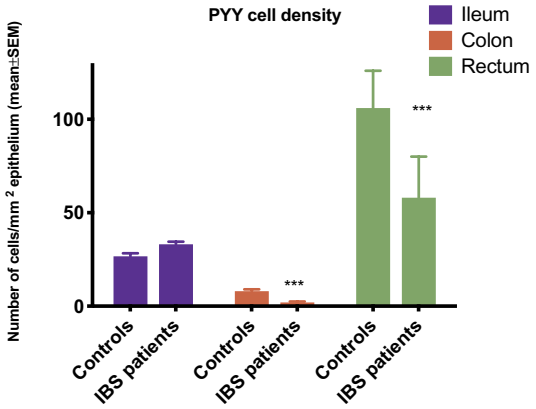

Fig. 2. The density of PYY cells in the ileum, colon and rectum of healthy subjects and patients with IBS. ***, < 0.001. Data from (El-Salhy et al., 2014c; El-Salhy et al., 2012a; El-Salhy and Gilja, 2017; El-Salhy et al., 2014a).

et al., 2015). Thus, PYY cells possess the elements necessary for both afferent and efferent synaptic transmission (Bohorquez et al., 2015). These findings suggest that PYY released in the lamina propria could act locally on close-by cells or neurons (in paracrine mode), via the circulating blood (in endocrine mode), or by afferent and efferent synaptic transmission (Fig. 1).

The density of PYY cells differs considerably between the rectum, colon and ileum, being highest in the rectum followed by the ileum and then the colon. It is known that PYY and oxyntomodulin (enteroglucagon) as well as glucagon-like peptide 1 (GLP-1) are produced from the same endocrine cell (L cells) (Habib et al., 2013; Spangeus et al., 2000). In this aspect PYY cells are similar to other enteroendocrine cells, which are capable of expressing up to seven different hormones (Egerod et al., 2012; Mortensen et al., 2003; Pyarokhil et al., 2012).

PYY belongs to the neuropeptide Y (NPY) family that comprises PYY, NPY and pancreatic polypeptide (Adrian et al., 1985; Tatemoto, 1982a, 1982b; Tatemoto and Mutt, 1980; Tatemoto et al., 1985). These three structurally related peptides consist of 36 amino-acid residues and act as hormones and/or neurotransmitters/neuromodulators (Vona-Davis and McFadden, 2007). PYY and the other two members of the NPY family exert their functions through binding to at least six Y-receptor subtypes of transmembrane-domain G-protein-coupled receptors (Vona-Davis and McFadden, 2007).

3. PYY regulatory functions and mode of action

PYY and NPY exert similar biological effects and bind to and activate receptors Y_1, Y_2 and Y_5 (Cox et al., 2001; Cox and Tough, 2002; Hyland and Cox, 2005; Hyland et al., 2003). Receptors Y_1 and Y_2 are localized in epithelial cells and submucosal and myenteric plexus neurons of the small intestine and colon (Cox et al., 2001; Cox and Tough, 2002; Gregor et al., 1996a; Gregor et al., 1996b; Gue et al., 1996; Inui et al., 1992; Mao et al., 1996; Sheikh and Williams, 1990; Walsh et al., 1993; Wharton et al., 1993; Yan et al., 1996). This explains why PYY and NPY exert similar effects in the gastrointestinal tract, although PPY is much more potent than NYY (Gomez et al., 1995).

PYY exert multiple physiological effects in the gastrointestinal tract. It delays gastric emptying, is a mediator of the ileal brake, inhibits gastric and pancreatic secretion, and stimulates the absorption of water and electrolytes (El-Salhy et al., 2014b; El-Salhy et al., 2012; Vona-Davis and McFadden, 2007). Furthermore, PYY seems to play an important role in modulating serotonin release from colonic enterochromaffin cells via the endogenous NK2/NK3 cascade system (Kojima et al., 2015). Serotonin is known to modulate visceral sensitivity and increase gastrointestinal motility and intestinal secretion (El-Salhy et al., 2012b; El-Salhy et al., 2012).

PPY also regulates the appetite and food intake (Konturek et al., 2004; Nguyen et al., 2011). PYY is released into the circulation in response to meal ingestion (Adrian et al., 1985), and a reduction in food consumption following the infusion of $PYY_{3–36}$ has been reported during test meals. Moreover, the plasma concentration of PYY is low in obese subjects (Batterham et al., 2003; Batterham et al., 2002). The arcuate nucleus (ARC) in the median eminence is the centre for integrating neurological and blood-borne signals (Cone et al., 2001; Peruzzo et al., 2000; Yu and Kim, 2012). The ARC lacks a complete blood–brain barrier and the brainstem is close to regions with an incomplete blood–brain barrier (Chaudhri et al., 2006; Yu and Kim, 2012). This allows both the ARC and brainstem to receive blood-borne signals, such as PYY. $PYY_{3–36}$ induces anorexia through binding to receptors Y_2 on the presynaptic terminals of hypothalamic NPY neurons so as to induce the inactivation of these neurons (Michel et al., 1998).

PYY also affects the appetite via its effect on the ileal brake by inhibiting food intake once nutrients have reached the ileum (Lin et al., 1996a, 1997; Lin et al., 1996b; Maljaars et al., 2007; Maljaars et al., 2008a; Maljaars et al., 2008b; Ohtani et al., 2001; Pironi et al., 1993; Van Citters and Lin, 1999, 2006).

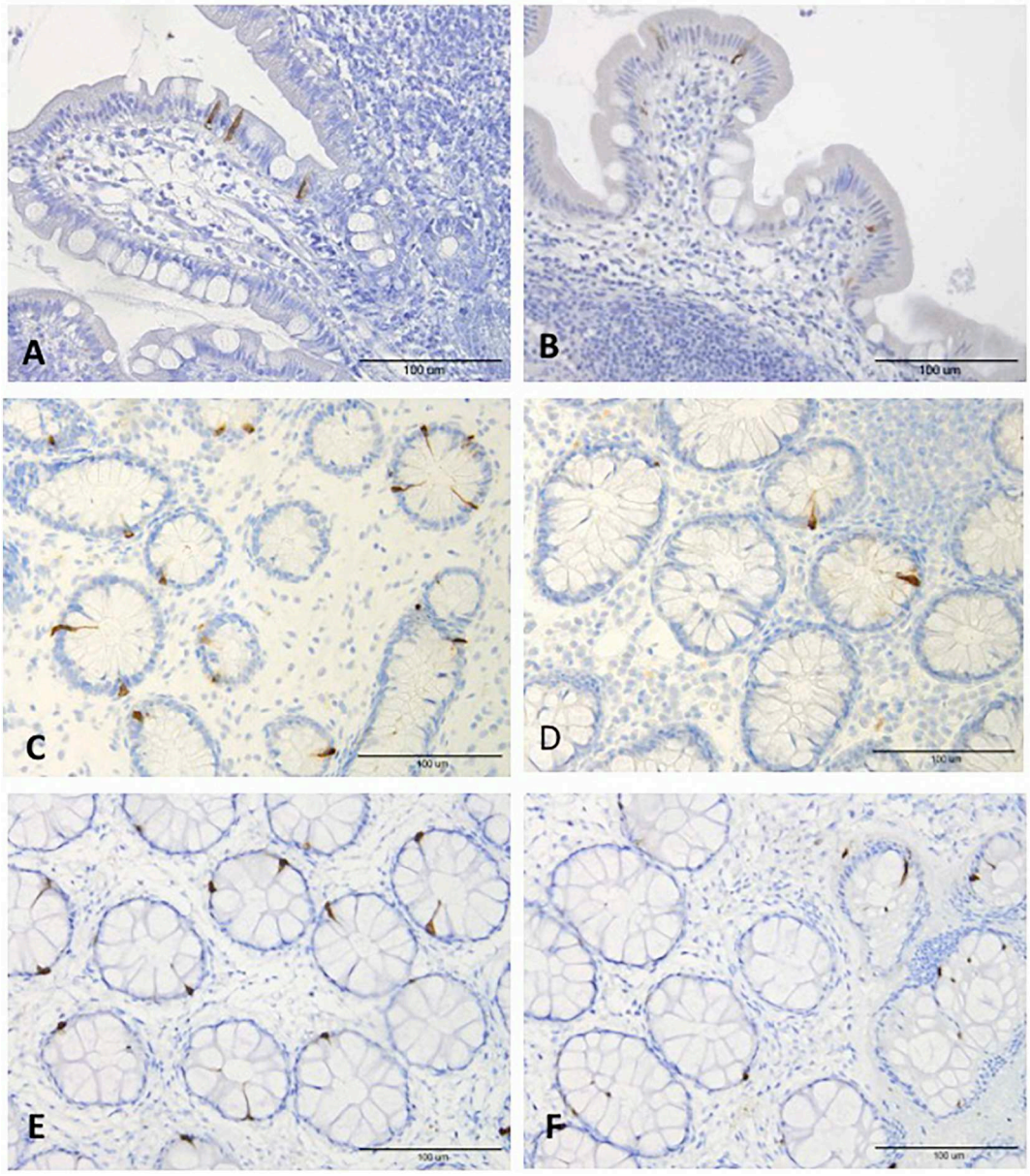

Fig. 3. PYY cells in the ileum, colon and rectum of healthy subjects (A, C and E) and patients with IBS (B, D and F). There were fewer PYY cells in the colon and rectum of IBS patients than in the healthy subjects.

4. Abnormalities in PYY in IBS

The density of PYY cells in the ileum does not differ between IBS patients and healthy subjects (Fig. 2) (El-Salhy and Gilja, 2017; El-Salhy et al., 2014a). However, the density of PYY cells and the concentration of PYY, as detected by radioimmunoassay, in colon are both lower in IBS patients than in healthy subjects (Figures and 3) (El-Salhy et al., 2014c; El-Salhy et al., 2012a; Simren et al., 2003). Similar to the colon, there are fewer PYY cells in the rectum of IBS patients than in healthy subjects (Fig. 4) (El-Salhy et al., 2012b). However, postprandial level of PYY did not differ from that of healthy subjects (Van Der Veek et al., 2006) Fig. 3.

The cell densities of Musashi 1 and neurogenin 3 in the colon are lower in IBS patients than in healthy subjects (El-Salhy et al., 2017; El-Salhy and Gilja, 2017) (Fig. 5). Musashi 1 is a marker for intestinal stem cells and their early progeny, while neurogenin 3 is a marker for early intestinal endocrine cell progenitors (Fishbein et al., 2009; He et al., 2007; Kayahara et al., 2003; Montgomery and Breault, 2008; Potten et al., 2003; Schonhoff et al., 2004a, 2004b). In patients with congenital malabsorptive diarrhoea and small-intestine allograft rejection, as well as in *NEUROG3*-knockout mice, the reduction in neurogenin 3 seems to result in a low density of enteroendocrine cells (Fishbein et al., 2009; Jenny et al., 2002; Wang et al., 2006). Accordingly, it can be speculated that changes in stem cells and enteroendocrine cells progenitors might

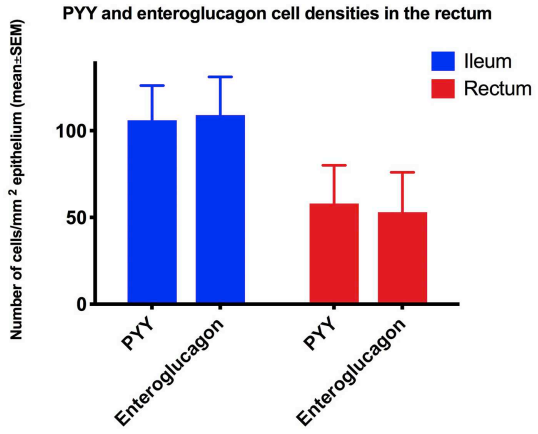

Fig. 4. The densities of PYY and oxyntomodulin (enteroglucagon) in the ileum and rectum of patients with IBS. There is no significant difference between the denities of PYY and oxyntomodulin cells. As L-cells express both PYY and oxyntomodulin, this shows that the low density of PYY cells is not caused by down regulating the expression of PYY and upp-regulating the expression of oxyntomodulin.

be responsible for the low density of PYY cells in the large intestine (El-Salhy et al., 2014d) (Fig. 6).

PYY cells express, as mentioned previously, also enteroglucagon (oxyntomodulin) and GLP-1. The density of the large intestinal enteroglucagon cells are significantly reduced in patients with IBS (El-Salhy et al., 2014c) (Fig. 4). Thus, the possibility that the reduction in the number of PYY cells is caused by switching off the synthesis of PYY and switching on the synthesis of enteroglucagon can be excluded (El-Salhy et al., 2017). Whether PYY cells switch off the synthesis of PYY and switch on the synthesis GLP-1 or other neuroendocrine peptides is unclear (Habib et al., 2013).

5. PYY role in the pathophysiology of IBS

Based on the current knowledge of the physiological functions of PYY in the gastrointestinal tract and the abnormalities seen in IBS, it can be hypothesized that a low PYY concentration and a low density of PYY cells in the large intestine would lead to a reduction in the amount of PYY released, with this in turn contributing to the dysmotility seen in IBS. Furthermore, since PYY modulates serotonin release, the low PYY concentration could contribute to the visceral hypersensitivity observed in IBS patients.

6. Clinical implications

Diet management of IBS patients involving consuming a low-FODMAP (fermentable oligo-, di-, and monosaccharides, and polyols) diet was found to restore their PYY cell density to the normal level (Mazzawi et al., 2015). This change was accompanied by an improvement in abdominal symptoms (Mazzawi et al., 2013). The interaction between dietary intake and the enteroendocrine cells is complicated (El-Salhy and Gundersen, 2015; El-Salhy et al., 2019). These changes in the density of PYY can be both cause and effect. The low density of PYY cells could be caused by the unsuitable intake of dietary items by Patients with IBS and restoring the density of these cells could be an effect of proper intake of food items (FODMAPs). The diet acts as a substrate for intestinal microbiota (prebiotic) and food items ingested determine the profile of the intestinal microbiota (El-Salhy et al., 2019). On the other hand, intestinal bacteria ferments the undigested food in the intestinal lumen, which results in fermentation by-products including short-chain fatty acids (SCFA) (El-Salhy et al., 2019). SCFA has been found to increase the secretion and upregulate the gene expression of PYY (Karaki et al., 2006; Samuel et al., 2008; Zhou et al., 2008). These observations suggest that diet management would be the best approach for correcting the PYY abnormalities seen in IBS patients in the clinic.

7. Conclusion

PYY plays an important role in regulating gastrointestinal motility, secretion and absorption, as well in the appetite. IBS patients have a low PYY concentration and also a low density of PYY cells in the large intestine compared to healthy subjects. These abnormalities seem to contribute to the dysmotility and visceral hypersensitivity seen in IBS patients. A PYY receptor agonist without serious side-effects would be ideal for IBS treatment. However, diet management appears to restore the PYY cell density in the large intestine seems to be the most appropriate approach to correct PYY abnormalities in the clinic.

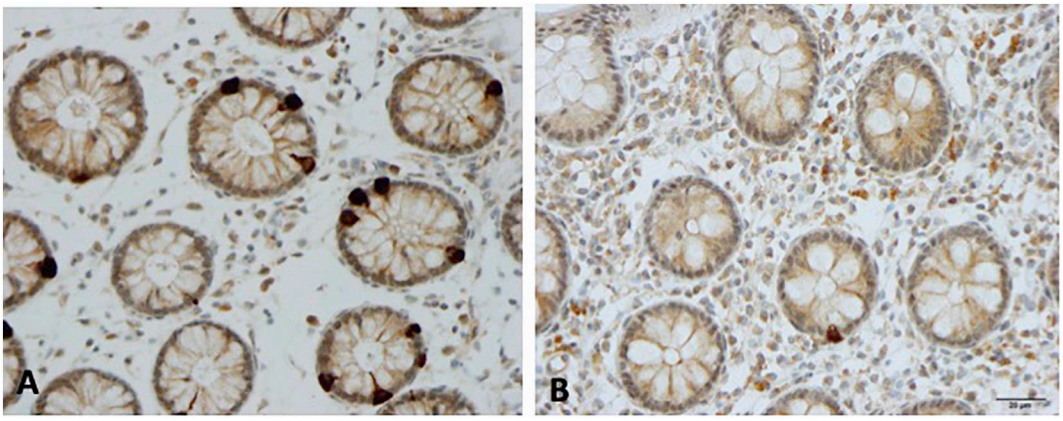

Fig. 5. Neurogenin 3 cells in the colon of a healthy subject (A) and in a patient with IBS (B). The density of neurogenin 3 is reduced in patients with IBS. The density of neurogenin 3 cells is lower in IBS patients than healthy subjects. Data from (El-Sahy et al., 2017)-.

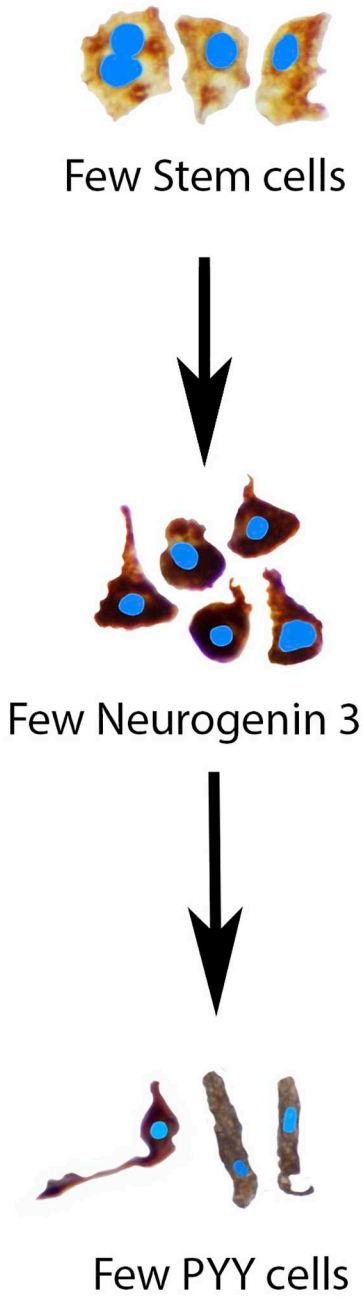

Fig. 6. Schematic of the possible cause of the low density of PYY cells in the large intestine of IBS patients. The decreased number of stem cells gives rise to fewer endocrine cell progenitors (neurogenin 3) cells, which in turn results in fewer PYY cells.

Acknowledgements

The studies performed by the authors cited in this review were supported by grants from Helse-Vest (grant no. 912234) and Helse-Fonna (grant no. 40415).

References

Adrian, T.E., Ferri, G.L., Bacarese-Hamilton, A.J., Fuessl, H.S., Polak, J.M., Bloom, S.R., 1985. Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterology 89, 1070–1077.

Agreus, L., Svardsudd, K., Nyren, O., Tibblin, G., 1995. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. Gastroenterology 109, 671–680.

Ansari, R., Attari, F., Razjouyan, H., Etemadi, A., Amjadi, H., Merat, S., Malekzadeh, R., 2008. Ulcerative colitis and irritable bowel syndrome: relationships with quality of life. Eur. J. Gastroenterol. Hepatol. 20, 46–50.

Batterham, R.L., Cowley, M.A., Small, C.J., Herzog, H., Cohen, M.A., Dakin, C.L., Wren, A.M., Brynes, A.E., Low, M.J., Ghatei, M.A., Cone, R.D., Bloom, S.R., 2002. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 418, 650–654.

Batterham, R.L., Cohen, M.A., Ellis, S.M., Le Roux, C.W., Withers, D.J., Frost, G.S., Ghatei, M.A., Bloom, S.R., 2003. Inhibition of food intake in obese subjects by peptide YY3-36. N. Engl. J. Med. 349, 941–948.

Bohorquez, D.V., Chandra, R., Samsa, L.A., Vigna, S.R., Liddle, R.A., 2011. Characterization of basal pseudopod-like processes in ileal and colonic PYY cells. J. Mol. Histol. 42, 3–13.

Bohorquez, D.V., Samsa, L.A., Roholt, A., Medicetty, S., Chandra, R., Liddle, R.A., 2014. An enteroendocrine cell-enteric glia connection revealed by 3D electron microscopy. PLoS One 9, e89881.

Bohorquez, D.V., Shahid, R.A., Erdmann, A., Kreger, A.M., Wang, Y., Calakos, N., Wang, F., Liddle, R.A., 2015. Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. J. Clin. Invest. 125, 782–786.

Chaudhri, O., Small, C., Bloom, S., 2006. Gastrointestinal hormones regulating appetite. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 361, 1187–1209.

Cone, R.D., Cowley, M.A., Butler, A.A., Fan, W., Marks, D.L., Low, M.J., 2001. The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. Int. J. Obes. Relat. Metab. Disord. 25 (Suppl. 5), S63–S67.

Cox, H.M., Tough, I.R., 2002. Neuropeptide Y, Y1, Y2 and Y4 receptors mediate Y agonist responses in isolated human colon mucosa. Br. J. Pharmacol. 135 (135), 1505–1512.

Cox, H.M., Pollock, E.L., Tough, I.R., Herzog, H., 2001. Multiple Y receptors mediate pancreatic polypeptide responses in mouse colon mucosa. Peptides 22, 445–452.

Drossman, D.A., Li, Z., Andruzzi, E., Temple, R.D., Talley, N.J., Thompson, W.G., Whitehead, W.E., Janssens, J., Funch-Jensen, P., Corazziari, E., et al., 1993. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig. Dis. Sci. 38, 1569–1580.

Egerod, K.L., Engelstoft, M.S., Grunddal, K.V., Nohr, M.K., Secher, A., Sakata, I., Pedersen, J., Windelov, J.A., Fuchtbauer, E.M., Olsen, J., Sundler, F., Christensen, J.P., Wierup, N., Olsen, J.V., Holst, J.J., Zigman, J.M., Poulsen, S.S., Schwartz, T.W., 2012. A major lineage of enteroendocrine cells coexpress CCK, secretin, GIP, GLP-1, PYY, and neurotensin but not somatostatin. Endocrinology 153, 5782–5795.

El-Sahy, M., Patcharatrakul, T., Hatlebakk, J.G., Hausken, T., Gilja, O.H., Gonlachanvit, S., 2017. Enteroendocrine, musashi 1, and neurogenin 3 cells in the large intestine of Thai and Norwegian patients with irritable bowel syndrome. Scand J Gastroenterol. 52, 1331–1339.

El-Salhy, M., 1984. Immunocytochemical investigation of the gastro-entero-pancreatic (GEP) neurohormonal peptides in the pancreas and gastrointestinal tract of the dogfish *Squalus acanthias*. Histochemistry 80, 193–205.

El-Salhy, M., 2012. Irritable bowel syndrome: diagnosis and pathogenesis. World J. Gastroenterol. 18, 5151–5163.

El-Salhy, M., 2015. Recent developments in the pathophysiology of irritable bowel syndrome. World J. Gastroenterol. 21, 7621–7636.

El-Salhy, M., Gilja, O.H., 2017. Abnormalities in ileal stem, neurogenin 3, and enteroendocrine cells in patients with irritable bowel syndrome. BMC Gastroenterol. 17, 90.

El-Salhy, M., Gundersen, D., 2015. Diet in irritable bowel syndrome. Nutr. J. 14, 36.

El-Salhy, M., Grimelius, L., Wilander, E., Abu-Sinna, G., Lundqvist, G., 1981. Histological and immunohistochemical studies of the endocrine cells of the gastrointestinal mucosa of the toad (Bufo regularis). Histochemistry 71, 53–65.

El-Salhy, M., Wilander, E., Grimelius, L., Terenius, L., Lundberg, J.M., Tatemoto, K., 1982. The distribution of polypeptide YY (PYY) - and pancreatic polypeptide (PP) - immunoreactive cells in the domestic fowl. Histochemistry 75, 25–30.

El-Salhy, M., Grimelius, L., Wilander, E., Ryberg, B., Terenius, L., Lundberg, J.M., Tatemoto, K., 1983a. Immunocytochemical identification of polypeptide YY (PYY) cells in the human gastrointestinal tract. Histochemistry 77, 15–23.

El-Salhy, M., Wilander, E., Juntti-Berggren, L., Grimelius, L., 1983b. The distribution and ontogeny of polypeptide YY (PYY)- and pancreatic polypeptide (PP)-immunoreactive cells in the gastrointestinal tract of rat. Histochemistry 78, 53–60.

El-Salhy, M., Gundersen, D., Hatlebakk, J.G., Hausken, T., 2012a. High densities of serotonin and peptide YY cells in the colon of patients with lymphocytic colitis. World J. Gastroenterol. 18, 6070–6075.

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

El-Salhy, M., Gilja, O.H., Gundersen, D., Hatlebakk, J.G., Hausken, T., 2014a. Endocrine cells in the ileum of patients with irritable bowel syndrome. World J. Gastroenterol. 20, 2383–2391.

El-Salhy, M., Gundersen, D., Gilja, O.H., Hatlebakk, J.G., Hausken, T., 2014b. Is irritable bowel syndrome an organic disorder? World J. Gastroenterol. 20, 384–400.

El-Salhy, M., Gundersen, D., Hatlebakk, J.G., Gilja, O.H., Hausken, T., 2014c. Abnormal rectal endocrine cells in patients with irritable bowel syndrome. Regul. Pept. 188, 60–65.

El-Salhy, M., Hatlebakk, J.G., Gilja, O.H., Hausken, T., 2014d. Irritable bowel syndrome: recent developments in diagnosis, pathophysiology, and treatment. Expert Rev. Gastroenterol. Hepatol. 8, 435–443.

El-Salhy, M., Hatlebakk, J.G., Gilja, O.H., Hausken, T., 2015. The relation between celiac disease, nonceliac gluten sensitivity and irritable bowel syndrome. Nutr. J. 14, 92.

El-Salhy, M., Mazzawi, T., Gundersen, D., Hausken, T., 2012. Chromogranin A cell density in the rectum of patients with irritable bowel syndrome. Mol. Med. Rep. 6,

1223–1225.
El-Salhy, M., Mazzawi, T., Hausken, T., Hatlebakk, J.G., 2016. Interaction between diet and gastrointestinal endocrine cells. Biomed Rep. 4, 651–656.
El-Salhy, M., Solomon, T., Hausken, T., Gilja, O.H., Hatlebakk, J.G., 2017. Gastrointestinal neuroendocrine peptides/amines in inflammatory bowel disease. World J. Gasoenterol. 23, 5068–5086.
El-Salhy, M., Hatlebakk, J.G., Hausken, T., 2019. Diet in irritable bowel syndrome (IBS): interaction with gut microbiota and gut hormones. Nutrients 11.
Fishbein, T.M., Novitskiy, G., Lough, D.M., Matsumoto, C., Kaufman, S.S., Shetty, K., Zasloff, M., 2009. Rejection reversibly alters enteroendocrine cell renewal in the transplanted small intestine. Am. J. Transplant. 9, 1620–1628.
Furness, J.B., Kunze, W.A., Clerc, N., 1999. Nutrient tasting and signaling mechanisms in the gut. II. The intestine as a sensory organ: neural, endocrine, and immune responses. Am. J. Phys. 277, G922–G928.
Furness, J.B., Rivera, L.R., Cho, H.J., Bravo, D.M., Callaghan, B., 2013. The gut as a sensory organ. Nature reviews. Gastroenterol. Hepatol. 10, 729–740.
Gomez, G., Zhang, T., Rajaraman, S., Thakore, K.N., Yanaihara, N., Townsend Jr., C.M., Thompson, J.C., Greeley, G.H., 1995. Intestinal peptide YY: ontogeny of gene expression in rat bowel and trophic actions on rat and mouse bowel. Am. J. Phys. 268, G71–G81.
Gregor, P., Feng, Y., DeCarr, L.B., Cornfield, L.J., McCaleb, M.L., 1996a. Molecular characterization of a second mouse pancreatic polypeptide receptor and its inactivated human homologue. J. Biol. Chem. 271, 27776–27781.
Gregor, P., Millham, M.L., Feng, Y., DeCarr, L.B., McCaleb, M.L., Cornfield, L.J., 1996b. Cloning and characterization of a novel receptor to pancreatic polypeptide, a member of the neuropeptide Y receptor family. FEBS Lett. 381, 58–62.
Gue, M., Junien, J.L., Reeve Jr., J.R., Rivier, J., Grandt, D., Tache, Y., 1996. Reversal by NPY, PYY and 3-36 molecular forms of NPY and PYY of intracisternal CRF-induced inhibition of gastric acid secretion in rats. Br. J. Pharmacol. 118, 237–242.
Habib, A.M., Richards, P., Rogers, G.J., Reimann, F., Gribble, F.M., 2013. Co-localisation and secretion of glucagon-like peptide 1 and peptide YY from primary cultured human L cells. Diabetologia 56, 1413–1416.
He, X.C., Yin, T., Grindley, J.C., Tian, Q., Sato, T., Tao, W.A., Dirisina, R., Porter-Westpfahl, K.S., Hembree, M., Johnson, T., Wiedemann, L.M., Barrett, T.A., Hood, L., Wu, H., Li, L., 2007. PTEN-deficient intestinal stem cells initiate intestinal polyposis. Nat. Genet. 39, 189–198.
Hyland, N.P., Cox, H.M., 2005. The regulation of veratridine-stimulated electrogenic ion transport in mouse colon by neuropeptide Y (NPY), Y1 and Y2 receptors. Br. J. Pharmacol. 146, 712–722.
Hyland, N.P., Sjoberg, F., Tough, I.R., Herzog, H., Cox, H.M., 2003. Functional consequences of neuropeptide Y Y 2 receptor knockout and Y2 antagonism in mouse and human colonic tissues. Br. J. Pharmacol. 139, 863–871.
Inui, A., Sano, K., Miura, M., Hirosue, Y., Nakajima, M., Okita, M., Baba, S., Kasuga, M., 1992. Evidence for further heterogeneity of the receptors for neuropeptide-Y and peptide-YY in tumor cell lines derived from neural crest. Endocrinology 131, 2090–2096.
Isgar, B., Harman, M., Kaye, M.D., Whorwell, P.J., 1983. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. Gut 24, 190–192.
Jenny, M., Uhl, C., Roche, C., Duluc, I., Guillermin, V., Guillemot, F., Jensen, J., Kedinger, M., Gradwohl, G., 2002. Neurogenin3 is differentially required for endocrine cell fate specification in the intestinal and gastric epithelium. EMBO J. 21, 6338–6347.
Karaki, S., Mitsui, R., Hayashi, H., Kato, I., Sugiya, H., Iwanaga, T., Furness, J.B., Kuwahara, A., 2006. Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. Cell Tissue Res. 324, 353–360.
Kayahara, T., Sawada, M., Takaishi, S., Fukui, H., Seno, H., Fukuzawa, H., Suzuki, K., Hiai, H., Kageyama, R., Okano, H., Chiba, T., 2003. Candidate markers for stem and early progenitor cells, Musashi-1 and Hes1, are expressed in crypt base columnar cells of mouse small intestine. FEBS Lett. 535, 131–135.
Keohane, J., O'Mahony, C., O'Mahony, L., O'Mahony, S., Quigley, E.M., Shanahan, F., 2010. Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association or reflection of occult inflammation? Am. J. Gastroenterol. 105 (1788), 1789–1794 (quiz 1795).
Kojima, S., Tohei, A., Ikeda, M., Anzai, N., 2015. An endogenous tachykinergic NK2/NK3 receptor cascade system controlling the release of serotonin from colonic mucosa. Curt. Neuropharmacol. 13, 830–835.
Konturek, S.J., Konturek, J.W., Pawlik, T., Brzozowski, T., 2004. Brain-gut axis and its role in the control of food intake. J. Physiol. Pharmacol. 55, 137–154.
Lin, H.C., Zhao, X.T., Wang, L., 1996a. Jejunal brake: inhibition of intestinal transit by fat in the proximal small intestine. Dig. Dis. Sci. 41, 326–329.
Lin, H.C., Zhao, X.T., Wang, L., Wong, H., 1996b. Fat-induced ileal brake in the dog depends on peptide YY. Gastroenterology 110, 1491–1495.
Lin, H.C., Zhao, X.T., Wang, L., 1997. Intestinal transit is more potently inhibited by fat in the distal (ileal brake) than in the proximal (jejunal brake) gut. Dig. Dis. Sci. 42, 19–25.
Maljaars, J., Peters, H.P., Masclee, A.M., 2007. Review article: the gastrointestinal tract: neuroendocrine regulation of satiety and food intake. Aliment. Pharmacol. Ther. 26 (Suppl. 2), 241–250.
Maljaars, P.W., Peters, H.P., Mela, D.J., Masclee, A.A., 2008a. Ileal brake: a sensible food target for appetite control. A review. Physiol. Behav. 95, 271–281.
Maljaars, P.W., Symersky, T., Kee, B.C., Haddeman, E., Peters, H.P., Masclee, A.A., 2008b. Effect of ileal fat perfusion on satiety and hormone release in healthy volunteers. Int. J. Obes. (Lond) 2005 (32), 1633–1639.
Mao, Y.K., Wang, Y.F., Ward, G., Cipris, S., Daniel, E.E., McDonald, T.J., 1996. Peptide YY receptor in submucosal and myenteric plexus synaptosomes of canine small intestine. Am. J. Phys. 271, G36–G41.
Mazzawi, T., Hausken, T., Gundersen, D., El-Salhy, M., 2013. Effects of dietary guidance on the symptoms, quality of life and habitual dietary intake of patients with irritable bowel syndrome. Mol. Med. Rep. 8, 845–852.
Mazzawi, T., Hausken, T., Gundersen, D., El-Salhy, M., 2015. Normalization of large intestinal endocrine cells following dietary management in patients with irritable bowel syndrome. Eur. J. Clin. Nutr. 70, 175–181.
Michel, M.C., Beck-Sickinger, A., Cox, H., Doods, H.N., Herzog, H., Larhammar, D., Quirion, R., Schwartz, T., Westfall, T., 1998. XVI. International union of pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY, and pancreatic polypeptide receptors. Pharmacol. Rev. 50, 143–150.
Minderhoud, I.M., Oldenburg, B., Wismeijer, J.A., van Berge Henegouwen, G.P., Smout, A.J., 2004. IBS-like symptoms in patients with inflammatory bowel disease in remission; relationships with quality of life and coping behavior. Dig. Dis. Sci. 49, 469–474.
Montgomery, R.K., Breault, D.T., 2008. Small intestinal stem cell markers. J. Anat. 213, 52–58.
Mortensen, K., Christensen, L.L., Holst, J.J., Orskov, C., 2003. GLP-1 and GIP are colocalized in a subset of endocrine cells in the small intestine. Regul. Pept. 114, 189–196.
Nguyen, A.D., Herzog, H., Sainsbury, A., 2011. Neuropeptide Y and peptide YY: important regulators of energy metabolism. Curr. Opin. Endocrinol. Diabetes Obes. 18, 56–60.
Ohtani, N., Sasaki, I., Naito, H., Shibata, C., Matsuno, S., 2001. Mediators for fat-induced ileal brake are different between stomach and proximal small intestine in conscious dogs. J. Gastrointest. Surg. 5 (5), 377–382.
Peruzzo, B., Pastor, F.E., Blazquez, J.L., Schobitz, K., Pelaez, B., Amat, P., Rodriguez, E.M., 2000. A second look at the barriers of the medial basal hypothalamus. Exp. Brain Res. 132, 10–26.
Pironi, L., Stanghellini, V., Miglioli, M., Corinaldesi, R., De Giorgio, R., Ruggeri, E., Tosetti, C., Poggioli, G., Morselli Labate, A.M., Monetti, N., et al., 1993. Fat-induced ileal brake in humans: a dose-dependent phenomenon correlated to the plasma levels of peptide YY. Gastroenterology 105, 733–739.
Potten, C.S., Booth, C., Tudor, G.L., Booth, D., Brady, G., Hurley, P., Ashton, G., Clarke, R., Sakakibara, S., Okano, H., 2003. Identification of a putative intestinal stem cell and early lineage marker; musashi-1. Differentiation 71, 28–41.
Pyarokhil, A.H., Ishihara, M., Sasaki, M., Kitamura, N., 2012. The developmental plasticity of colocalization pattern of peptide YY and glucagon-like peptide-1 in the endocrine cells of bovine rectum. Biomed. Res. 33, 35–38.
Samuel, B.S., Shaito, A., Motoike, T., Rey, F.E., Backhed, F., Manchester, J.K., Hammer, R.E., Williams, S.C., Crowley, J., Yanagisawa, M., Gordon, J.I., 2008. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc. Natl. Acad. Sci. U. S. A. 105, 16767–16772.
Schonhoff, S.E., Giel-Moloney, M., Leiter, A.B., 2004a. Minireview: development and differentiation of gut endocrine cells. Endocrinology 145, 2639–2644.
Schonhoff, S.E., Giel-Moloney, M., Leiter, A.B., 2004b. Neurogenin 3-expressing progenitor cells in the gastrointestinal tract differentiate into both endocrine and non-endocrine cell types. Dev. Biol. 270, 443–454.
Sheikh, S.P., Williams, J.A., 1990. Structural characterization of Y1 and Y2 receptors for neuropeptide Y and peptide YY by affinity cross-linking. J. Biol. Chem. 265, 8304–8310.
Simren, M., Axelsson, J., Gillberg, R., Abrahamsson, H., Svedlund, J., Bjornsson, E.S., 2002. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. Am. J. Gastroenterol. 97, 389–396.
Simren, M., Stotzer, P.O., Sjovall, H., Abrahamsson, H., Bjornsson, E.S., 2003. Abnormal levels of neuropeptide Y and peptide YY in the colon in irritable bowel syndrome. Eur. J. Gastroenterol. Hepatol. 15, 55–62.
Spangeus, A., Forsgren, S., El-Salhy, M., 2000. Does diabetic state affect co-localization of peptide YY and enteroglucagon in colonic endocrine cells? Histol. Histopathol. 15, 37–41.
Tatemoto, K., 1982a. Isolation and characterization of peptide YY (PYY), a candidate gut hormone that inhibits pancreatic exocrine secretion. Proc. Natl. Acad. Sci. U. S. A. 79, 2514–2518.
Tatemoto, K., 1982b. Neuropeptide Y: complete amino acid sequence of the brain peptide. Proc. Natl. Acad. Sci. U. S. A. 79, 5485–5489.
Tatemoto, K., Mutt, V., 1980. Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. Nature 285, 417–418.
Tatemoto, K., Siimesmaa, S., Jornvall, H., Allen, J.M., Polak, J.M., Bloom, S.R., Mutt, V., 1985. Isolation and characterization of neuropeptide Y from porcine intestine. FEBS Lett. 179, 181–184.
Van Citters, G.W., Lin, H.C., 1999. The ileal brake: a fifteen-year progress report. Curr. Gastroenterol. Rep. 1, 404–409.
Van Citters, G.W., Lin, H.C., 2006. Ileal brake: neuropeptidergic control of intestinal transit. Curr. Gastroenterol. Rep. 8, 367–373.
Van Der Veek, P.P., Biemond, I., Masclee, A.A., 2006. Proximal and distal gut hormone secretion in irritable bowel syndrome. Scand. J. Gastroenterology 41, 170–177.
Vona-Davis, L.C., McFadden, D.W., 2007. NPY family of hormones: clinical relevance and potential use in gastrointestinal disease. Curr. Top. Med. Chem. 7, 1710–1720.
Walsh, D.A., Wharton, J., Blake, D.R., Polak, J.M., 1993. Localization and

characterization of neuropeptide Y binding sites in porcine and human colon. Br. J. Pharmacol. 108, 304–311.
Wang, J., Cortina, G., Wu, S.V., Tran, R., Cho, J.H., Tsai, M.J., Bailey, T.J., Jamrich, M., Ament, M.E., Treem, W.R., Hill, I.D., Vargas, J.H., Gershman, G., Farmer, D.G., Reyen, L., Martin, M.G., 2006. Mutant neurogenin-3 in congenital malabsorptive diarrhea. N. Engl. J. Med. 355, 270–280.
Wharton, J., Gordon, L., Byrne, J., Herzog, H., Selbie, L.A., Moore, K., Sullivan, M.H., Elder, M.G., Moscoso, G., Taylor, K.M., et al., 1993. Expression of the human neuropeptide tyrosine Y1 receptor. Proc. Natl. Acad. Sci. U. S. A. 90, 687–691.
Yan, H., Yang, J., Marasco, J., Yamaguchi, K., Brenner, S., Collins, F., Karbon, W., 1996. Cloning and functional expression of cDNAs encoding human and rat pancreatic polypeptide receptors. Proc. Natl. Acad. Sci. U. S. A. 93, 4661–4665.
Yu, J.H., Kim, M.S., 2012. Molecular mechanisms of appetite regulation. Diabetes Metab. J. 36, 391–398.
Zhou, J., Martin, R.J., Tulley, R.T., Raggio, A.M., McCutcheon, K.L., Shen, L., Danna, S.C., Tripathy, S., Hegsted, M., Keenan, M.J., 2008. Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents. Am. J. Physiol. Endocrinol. Metab. 295, E1160–E1166.