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

Magdy El-Salhy\textsuperscript{a,b,c,}\textsuperscript{*}, Jan Gunnar Hatlebakk\textsuperscript{b,c}, Trygve Hausken\textsuperscript{b,c}

\textsuperscript{a} Section for Gastroenterology, Department of Medicine, Stord Hospital, Stord, Norway
\textsuperscript{b} Department of Clinical Medicine, University of Bergen, Bergen, Norway
\textsuperscript{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 etiology 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; Tatamoto, 1982a; Tatamoto 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 (El-Salhy et al., 1984; El-Salhy et al., 1981; El-Salhy et al., 1982; El-Salhy et al., 1983b).

Different pathogens—such as E. coli, Salmonella, Shigella, and Clostridium difficile—can cause IBS symptoms via a paracrine mechanism (Furness et al., 1999; Furness et al., 2013). The paracrine mechanism of PYY may therefore contribute to the intestinal dysmotility and visceral hypersensitivity seen in IBS patients. 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.
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 Y1, Y2 and Y5 (Cox et al., 2001; Cox and Tough, 2002; Hyland and Cox, 2005; Hyland et al., 2003). Receptors Y1 and Y2 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 PYY is much more potent than NYY (Gomez et al., 1995).

PYY exerts 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., 2012a; El-Salhy et al., 2012).

PYY 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 PYY3–36 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. PYY3–36 induces anorexia through binding to receptors Y2 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).
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 3) (El-Salhy et al., 2014c; El-Salhy et al., 2012a; Simren et al., 2003). Similarly 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 density 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...
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.
Few Stem cells

Few Neurogenin 3 cells

Few PYY cells

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


