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The role of the neuropeptide Y (NPY) family in the pathophysiology of inflammatory bowel disease (IBD)

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ABSTRACT

Inflammatory bowel disease (IBD) includes three main disorders: ulcerative colitis, Crohn's disease, and microscopic colitis. The etiology of IBD is unknown and the current treatments are not completely satisfactory. Interactions between the gut neurohormones and the immune system are thought to play a pivot role in inflammation, especially in IBD. These neurohormones are believed to include members of the neuropeptide YY (NPY) family, which comprises NPY, peptide YY (PYY), and pancreatic polypeptide (PP). Understanding the role of these peptides may shed light on the pathophysiology of IBD and potentially yield an effective treatment tool. Intestinal NPY, PYY, and PP are abnormal in both patients with IBD and animal models of human IBD. The abnormality in NPY appears to be primarily caused by an interaction between immune cells and the NPY neurons in the enteric nervous system; the abnormalities in PYY and PP appear to be secondary to the changes caused by the abnormalities in other gut neurohormonal peptides/amines that occur during inflammation. NPY is the member of the NPY family that can be targeted in order to decrease the inflammation present in IBD.

Contents

1. Introduction

Inflammatory bowel disease (IBD) comprises three main disorders: ulcerative colitis (UC), Crohn's disease (CD), and microscopic colitis (MC). These disorders exhibit distinct clinical courses, organ specificities, and histopathological features (El-Salhy et al. 2012a, 2013a). UC, CD, and MC are chronic diseases; and while UC and CD patients experience infrequent relapses with years of complete remission, frequent relapses, or chronic active disease, MC patients typically experience chronic active disease (Danese and Fiocchi 2006; El-Salhy et al. 2013a; Nunes et al. 2011). The inflammation in CD is transmural in nature and occurs in any part of the gastrointestinal tract, while the inflammation in UC is more superficial and affects the rectocolonic mucosa, and the inflammation in MC manifests as mucosal and submucosal infiltration of immune cells without ulcerations or crypt abscesses and occurs in the colon (El-Salhy et al. 2012a, 2013a). In contrast to UC and CD, spontaneous symptomatic remission in MC has been reported to occur in 59–93% of the patients (Baert et al. 1999; Mullhaupt et al. 1998). The onset of UC and CD occurs more commonly at a young age

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(i.e., <40 years), whereas the onset of MC generally occurs in the elderly (i.e., >60 years) (Carter et al. 2004; El-Salhy et al. 2013a). In addition to the morbidity associated with IBD, it has a marked negative impact on the quality of life (El-Salhy et al. 2013a; Podolsky 2002a, 2002b).

The etiology of IBD is unknown and the current treatments are not completely satisfactory (El-Salhy et al. 2012a, 2013a). Treatments with 5-aminosalicylates and corticosteroids are not effective for most patients over the long term (El-Salhy et al. 2012a), and the short- and long-term side effects of the thiopurine analogs mercaptopurine, azathioprine, and methotrexate restrict their use (El-Salhy et al. 2012a). Biological agents such as antibodies against tumor necrosis factor (TNF) α are effective in only about 65% of UC and CD patients. Surgical treatment can result in malnutrition and eventual short-bowel syndrome in CD patients, and severe diarrhea in UC patients (El-Salhy et al. 2012a).

The interaction between the neuroendocrine peptides/amines of the gut and the immune system has been the focus of recent research, and it has been suggested that this interaction plays an important role in the pathophysiology of IBD (Ameri and Ferone 2012; Bampton and Dinning 2013; Farzi et al. 2015; Khan and Ghia 2010; Margolis and Gershon 2009). It is believed that an improved understanding of the role of the gut neuroendocrine peptides/amines in IBD will lead to the application of agonists or antagonists to these peptides/amines that represent a potentially significant therapeutic opportunity in IBD. The role of the neuropeptide Y (NPY) family in IBD has been discussed previously (El-Salhy et al. 2013b; El-Salhy et al. 2002; Vona-Davis and McFadden 2007; Wheway et al. 2007a, 2007b; Wheway et al. 2005). The present review summarizes the available data on the NPY family in IBD and speculates on its role in the pathophysiology of this disease.

2. The NPY family of peptides

The NPY family comprises three peptides—namely NPY, peptide YY (PYY), and pancreatic polypeptide (PP) (Adrian et al. 1985; Tatemoto 1982a, 1982b; Tatemoto and Mutt 1980; Tatemoto et al. 1985)—that act as hormones and/or neurotransmitters/neuromodulators. These peptides consists of 36 amino acid residues and are structurally related (Vona-Davis and McFadden 2007). NPY is expressed in multiple neuronal systems of the brain, from the medullary brainstem to the cerebral cortex, and in enteric neurons including secretomotor and inhibitory motoneurones (Brumovsky et al. 2007; Eaton et al. 2007; Kask et al. 2002; Tatemoto 1982b; Tatemoto et al. 1985; Vona-Davis and McFadden 2007; Wettstein et al. 1995), while PYY and PP are localized in endocrine cells in the ileum, colon, and rectum (El-Salhy et al. 1983a; El-Salhy et al. 1982; El-Salhy et al. 1983b). PP is also found in endocrine cells in the pancreatic islets of Langerhans (Adrian et al. 1985).

All three peptides belonging to the NPY family exert their actions by binding to at least six Y-receptor subtypes of transmembrane G-protein-coupled receptors (Vona-Davis and McFadden 2007). Five Y receptors are expressed in mammals (including humans), namely Y_1, Y_2, Y_4, Y_5, and Y_6 (Farzi et al. 2015). NPY and PYY bind to and activate receptors Y_1, Y_2, and Y_5, and PP binds to receptor Y_4 (Cox et al. 2001; Cox and Tough 2002; Hyland and Cox 2005; Hyland et al. 2003). Receptors Y_1, Y_2, and Y_4 have been found in the colon and small intestine, localized to epithelial cells and neurons belonging to the submucosal and myenteric plexus (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).

The NPY family of peptides exerts multiple physiological effects upon binding to their receptors. NPY and PYY exert similar biological effects, which differ from the effects of PP. NPY and PYY delay gastric emptying and are mediators of the ileal brake; they also inhibit gastric and pancreatic secretion, and stimulate the absorption of water and electrolytes (El-Salhy et al. 2014; El-Salhy et al. 2012d; Vona-Davis and McFadden 2007). The effects of NPY in the gut are much less potent than those of PYY (Gomez et al. 1995). PP stimulates gastric acid secretion and the motility of the stomach and small intestine, relaxes the gallbladder, and inhibits pancreatic secretion (El-Salhy et al. 2014; El-Salhy et al. 2012d).

All members of the NPY peptide family play a pivotal role in regulating the appetite and food intake (Konturek et al. 2004; Nguyen et al. 2011). NPY is expressed in two populations of neurons in the arcuate nucleus (ARC) of the hypothalamus: (1) those expressing both NPY and AgRP (Agouti-related peptide), and (2) those containing NPY and POMC (the pro-opiomelanocortin and cocaine and amphetamine-regulated transcript)—the former neurons stimulate food intake while the latter suppress it (Ellacott and Cone 2004; Nguyen et al. 2011; Ollmann et al. 1997). The ARC lies in the median eminence, which lacks a complete blood–brain barrier and is thus susceptible to factors circulating in the blood (Cone et al. 2001; Peruzzo et al. 2000; Yu 2012). The ARC is the center for integrating neurological and blood-borne signals. Similarly, the brainstem is proximal to other regions with an incomplete blood–brain barrier, thus allowing it to receive blood-borne signals (Chaudhri et al. 2006; Yu 2012). PYY is released into the circulation in response to meal ingestion (Adrian et al. 1985). Infusing $PYY_{3\text{-}36}$ was found to reduce food consumption during test meals. Moreover, obese subjects were shown to have a low plasma level of PYY (Batterham et al. 2003; Batterham et al. 2002). Circulating $PYY_{3\text{-}36}$ binds to the Y_2 receptors on the presynaptic terminals of hypothalamic NPY neurons, inactivating them and resulting in the induction of anorexia (Michel et al. 1998). By regulating the ileal break, PYY inhibits further food intake once nutrients have reached the distal small intestine (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). Similar to PYY, PP reduces appetite and food intake (Jesudason et al. 2007; Zhang et al. 2012).

3. The NPY family and inflammation

The sympathetic neurons that innervate lymphoid organs contain NPY, which is co-released with norepinephrine upon stimulation (Lundberg et al. 1989; Romano et al. 1991). NPY is produced by T lymphocytes, macrophages, monocytes, and dendritic cells during inflammation, and it modulates the immune cell activities via a paracrine or autocrine mode of action (Macia et al. 2012; Schwarz et al. 1994; Wheway et al. 2005). The Y_1 and Y_2 receptors are localized on immune cells including macrophages, neutrophils, granulocytes, and lymphocytes, with the Y_1 receptor being the most abundant (Bedoui et al. 2008; Chandrasekharan et al. 2013b; Dimitrijevic et al. 2005; Dimitrijevic and Stanojevic 2013; Dimitrijevic et al. 2010; Singer et al. 2013). The binding of NPY to these receptors influences the activities of the immune cells (Farzi et al. 2015; Petitto et al. 1994) in either a pro- or an anti-inflammatory manner (Farzi et al. 2015; Wheway et al. 2005). NPY plays a distinctive role in the immunity of the gastrointestinal tract since NPY nerve fibers are in close contact with immune cells (Shibata et al. 2008), and there is compelling evidence that NPY exerts a proinflammatory action in the gut (Chandrasekharan et al. 2008; Chandrasekharan et al. 2013a; Farzi et al. 2015; Hassani et al. 2005; Holzer et al. 2012; Painsipp et al. 2011; Pang et al. 2010; Wheway et al. 2005).

PYY mRNA has been found in mouse macrophages (Macia et al. 2012), and PYY increases the adhesion of macrophages, chemotaxis, phagocytosis, and production of superoxide anions (De la Fuente et al. 1993). The exact role of PP in inflammation has not yet been determined.

4. Abnormalities in the NPY family in IBD

The induction of colitis in mice using either dextran sodium sulfate (DSS) or *Salmonella-typhimurium*-pretreated streptomycin lead to an increase in NPY enteric neurons and hyperplasia of NPY nerve fibers (Bjorck et al. 1997; Chandrasekharan et al. 2008). Surgical resection of

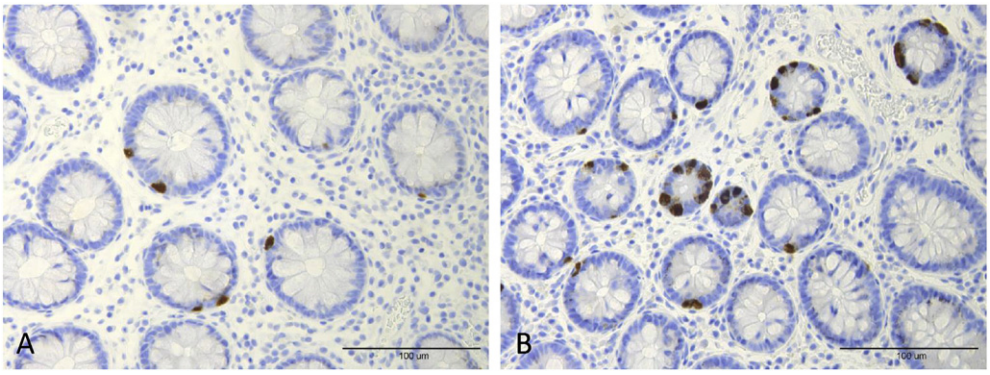

Fig. 1. PYY cells in the colon of a healthy subject (A) and in the colon of a patient with lymphocytic colitis (B).

the ileum of CD patients was shown to increase the density of NPY neurons in the myenteric plexus (Belai et al. 1997). The plasma levels of NPY were lower in patients with either CD or UC in remission or relapse than in controls, although the difference was not statistically significant (Fagerstam et al. 2000). The density of PYY cells is increased in patients with UC or MC (Fig. 1), in rats with DSS-induced colitis, and in interleukin (IL)-2-gene knock-out mice (Fig. 2) (El-Salhy et al. 1997; El-Salhy et al. 2012c; El-Salhy et al. 2015; Qian et al. 2000). The strong correlation between the densities of PYY cells and immune cells found in DSS-induced colitis in rats supports the presence of an interaction between these endocrine cells and the immune cells. The PP cell density is reduced in patients with UC and CD, and in rats with DSS-induced colitis (Fig. 3) (El-Salhy et al. 1997; El-Salhy et al. 2015).

IBD patients experience social and psychological stress, and the psychological stress negatively influences intestinal inflammation (Ghia et al. 2009a; Mittermaier et al. 2004). NPY plays a significant role in stress (Farzi et al. 2015), and it is reasonable to expect changes in brain NPY to be associated with IBD. Hyperreflexia of the autonomic nervous system has been reported in patients with CD and UC, with this hyperreflexia being significantly associated with the disease severity (Straub et al. 1997). Increases in TNF or IL-6 that occur during the inflammation in CD and UC activate the hypothalamus autonomic nervous system axis, as detected by NPY plasma levels, and the hypothalamic-pituitary-adrenal axis as measured by the serum cortisol levels (Straub et al. 2002). That study found a negative correlation between the serum cortisol and plasma NPY levels in IBD patients. Alterations of NPY, NPY receptor Y_1, and corticotropin-releasing hormone gene expression were detected in DSS-induced colitis in mice (Reichmann et al. 2015). Moreover, the combination of DSS-induced colitis and stress increased the levels of IL-6 and growth-regulated oncogene-α in the brain (Reichmann et al. 2015). An increase in circulating NPY and a decrease in the hippocampal expression of NPY mRNA were found in mice with DSS-induced colitis (Hassan et al. 2014). Repeated stress induced by water-avoidance tests in mice with DSS-induced colitis elevated the circulating corticosterone level and the expression of hypothalamic NPY mRNA (Hassan et al. 2014).

5. Role of the NPY family in IBD

During the inflammation process, the NPY-family peptides interact and integrate with other neurohormonal peptides of the gut such as substance P, vasoactive polypeptide, serotonin, and somatostatin. A more complete understanding of the role of the NPY-family peptides in IBD requires consideration of two other neurohormonal peptides: serotonin and somatostatin. An interaction between NPY and serotonin in the brain has been reported (Shibata et al. 2008; Shimizu and Bray 1989), and administering NPY into the ventromedial and lateral hypothalamus of rats decreased the concentration of serotonin and its metabolite 5-HIAA (Shimizu and Bray 1989). Injecting rats with a serotonin antagonist increased the level of hypothalamic NPY mRNA (Shibata et al. 2008). Serotonin is believed to play a pivotal role in intestinal inflammation (Khan and Ghia 2010; Spiller 2008). IL-13 receptors have been localized on serotonin cells (Wang et al. 2007), and serotonin receptors have been found in several immune cells including lymphocytes, monocytes, macrophages, and dendritic cells (Cloez-Tayarani and Changeux 2007). Serotonin also affects the proliferation of lymphocytes, protects natural killer cells, inhibits the apoptosis of immune cells, and promotes the recruitment of T cells (Betten et al. 2001; Laberge et al., 1996; Soga et al. 2007; Stefulj et al. 2001). The onset of DSS-induced colitis was delayed and its severity was decreased in mice deficient in tryptophan hydroxylase 1, and the level of serotonin in the gastrointestinal tract is reduced in these mice (Ghia et al. 2009b). Furthermore, restoring serotonin levels in this experimental model using the serotonin-precursor 5-hydroxytryptophan increased the severity of the DSS-induced colitis (Ghia et al. 2009b). Serotonin is considered to be proinflammatory during the inflammatory process. The

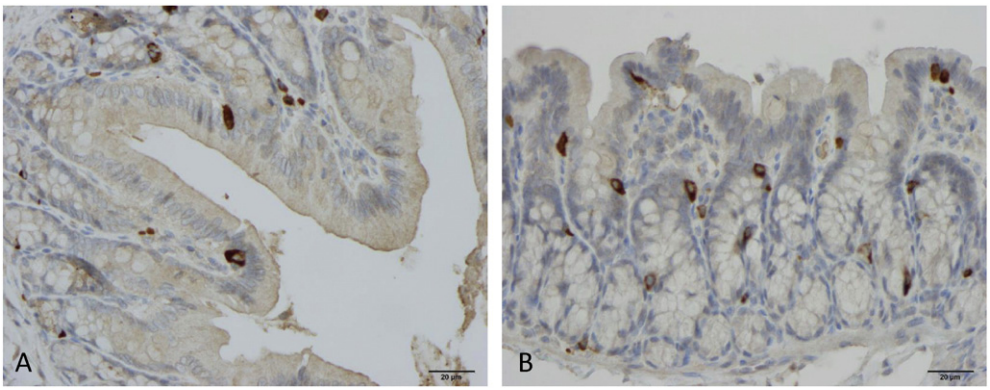

Fig. 2. Colonic PYY cells in a control rat (A) and in a rat with DSS-induced colitis (B).

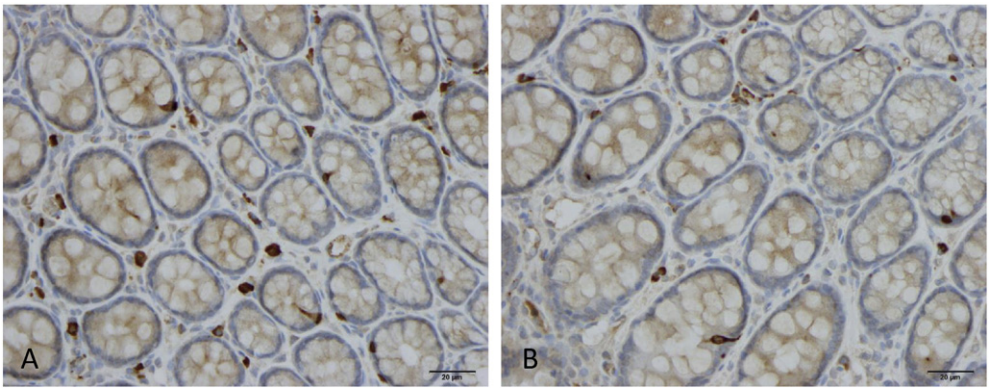

Fig. 3. PP cells in the colon of a control rat (A) and in the colon of a rat with DSS-induced colitis (B).

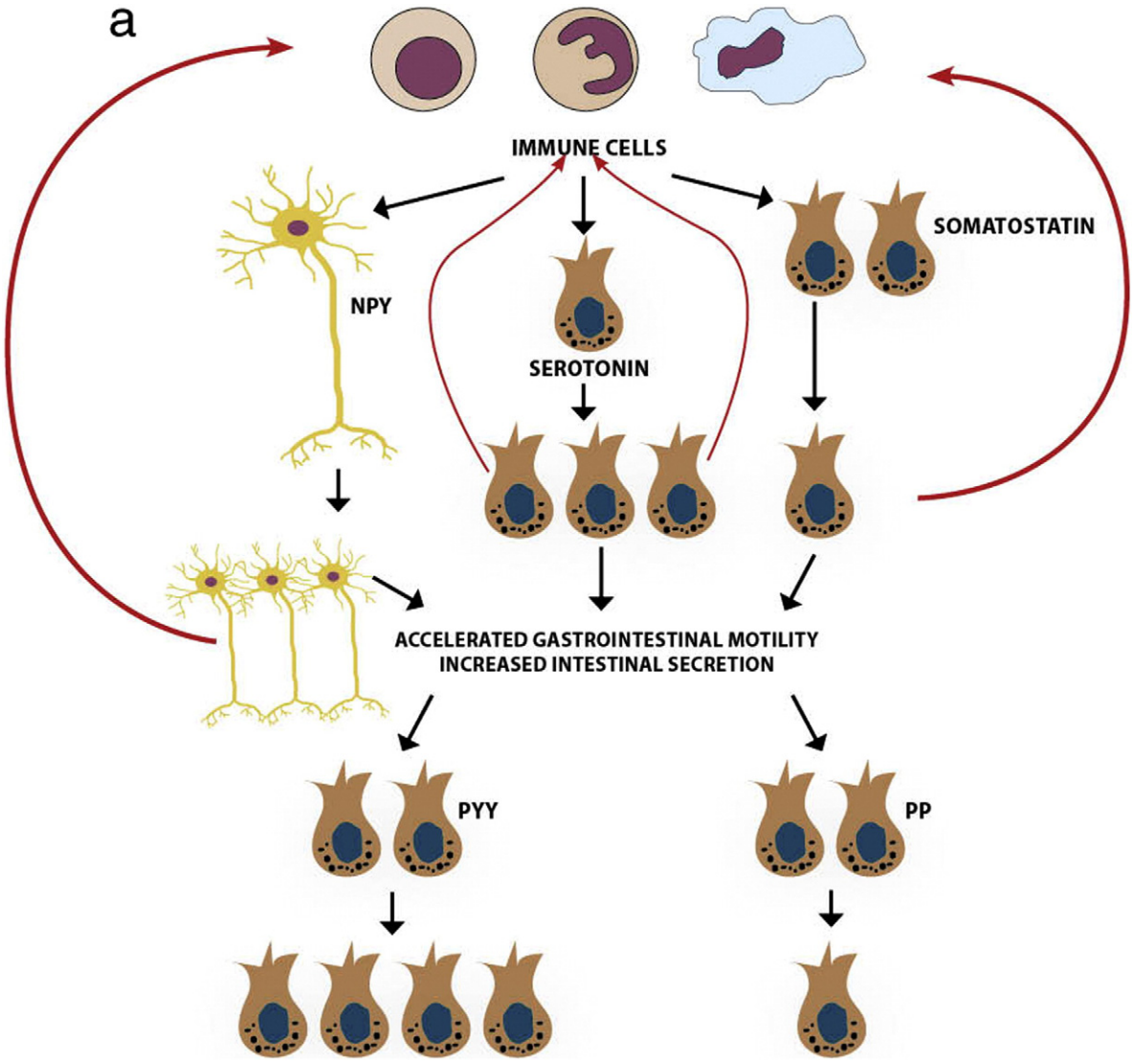

Fig. 4. A. Schematic of the possible role of members of the NPY family in the pathophysiology of IBD. The immune cells interact with NPY neurons in the enteric nervous system and with the mucosal serotonin and somatostatin cells. This interaction results in increased densities of NPY neurons and serotonin cells, as well as a decreased density of somatostatin cells—these changes would result in accelerated gastrointestinal motility and increased intestinal secretion (diarrhea). As a feedback response to increased gut motility and secretion, the density of mucosal PYY cells increases and that of PP cells decreases. B. Schematic of the possible consequences of administering an NPY receptor antagonist in IBD. Blocking the NPY receptors would decrease the proliferation of immune cells and the production of proinflammatory cytokines, which would in turn result in normal densities of NPY neurons and cells containing serotonin and somatostatin. The absence of changes in the densities of NPY cells, serotonin, and somatostatin would return the gastrointestinal motility and secretion normal, and so not stimulate any changes in PYY and PP cells.

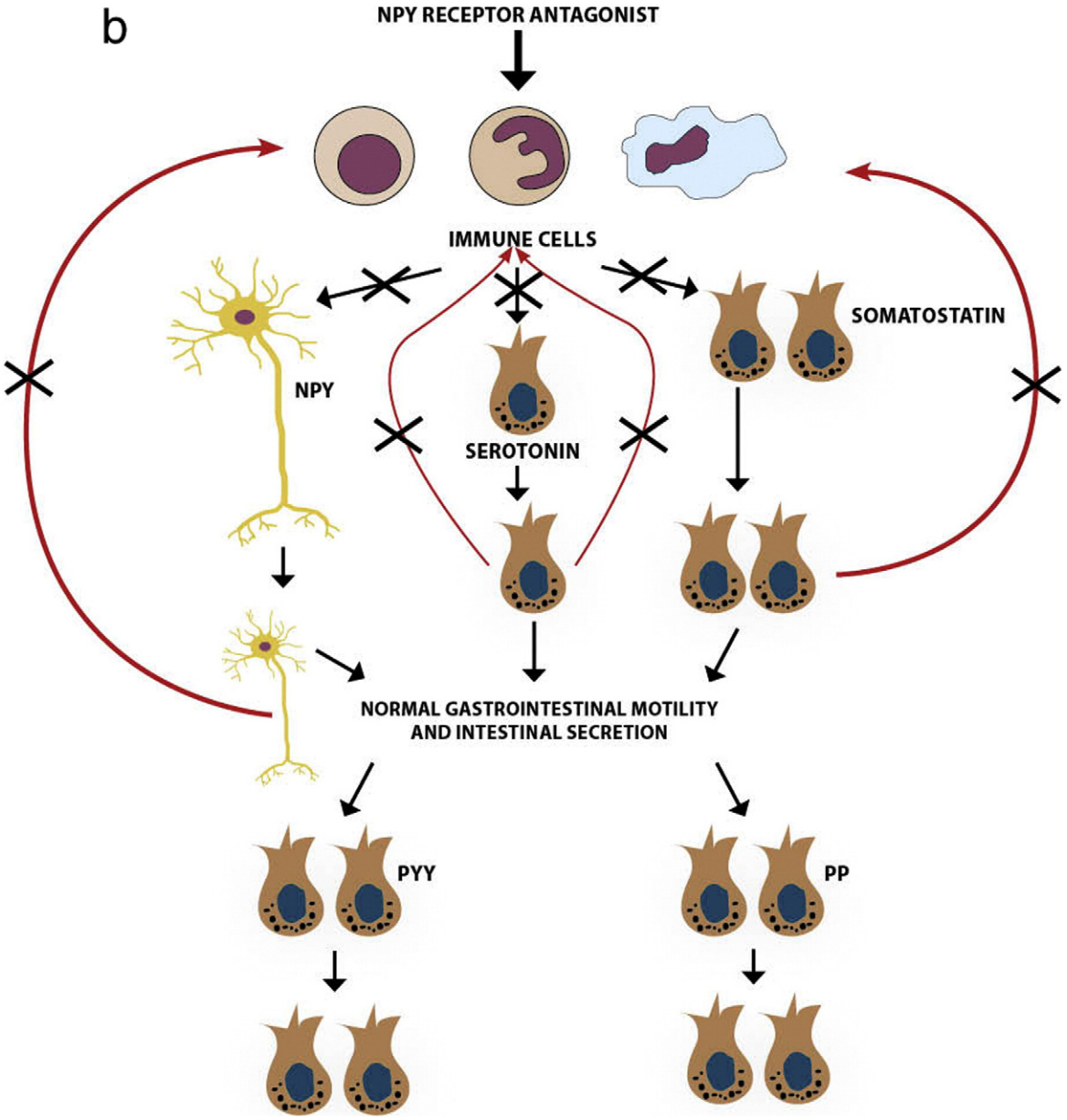

Fig. 4 (*continued*).

density of colonic serotonin has been reported to be high in patients with UC, CD, and MC, as well as in animal models of colitis (Bertrand and Bertrand 2010; El-Salhy et al. 1997; El-Salhy et al. 2012b; El-Salhy et al. 2015; Oshima et al. 1999; Qian et al. 2000). Serotonin stimulates gastric and intestinal motility, modulates visceral sensitivity, and stimulates intestinal secretion (El-Salhy et al. 2012c; El-Salhy et al. 2012d). The increase in serotonin in IBD may lead to increase gastric and intestinal motility as well as increased intestinal secretion.

Somatostatin exerts its actions by binding to five membrane G-protein-coupled receptors subtypes, which are designated as somatostatin receptors 1–5 (Ferone et al. 2005). Somatostatin receptors have been localized on different immune cells such as monocytes/macrophages, B lymphocytes, T lymphocytes, and dendritic cells (Armani et al. 2007; Dalm et al. 2003; Ferone et al. 2012; Ferone et al. 2002; Ferone et al. 2005; Hagstromer et al. 2006; Lichtenauer-Kaligis et al. 2004; Talme et al. 2001; Taniyama et al. 2005; ten Bokum et al. 2000). Somatostatin stimulates the proliferation of B lymphoblasts by enhancing the formation of immunoglobulins (Rosskopf et al. 2003), and inhibits T-lymphocyte proliferation and reduces the proinflammatory cytokines such as interferon-γ (Casnici et al. 1997; Radosevic-Stasic et al. 1995; Sirianni et al. 1994; ten Bokum et al. 2000). Somatostatin is considered to also exert anti-inflammatory effects (Ameri and Ferone 2012; Helyes et al. 2007; Helyes et al. 2009). The somatostatin cell density is decreased in the colon of patients with UC and CD, as well as in animal models of induced colitis (El-Salhy et al. 2015; Koch et al. 1988; Watanabe et al. 1992). Somatostatin inhibits intestinal motility, as well as gastrointestinal exocrine and neuroendocrine secretion (El-Salhy et al. 2012d). The decrease in somatostatin would result in the further acceleration of gastrointestinal motility and an increase in intestinal secretion.

Based on the data presented in this review, it can be speculated that the immune cells interact with NPY neurons, serotonin cells, and somatostatin cells during inflammation (Fig. 4A). This interaction results in increased densities of NPY neurons in the enteric nervous system and of serotonin cells in the mucosa, and a decrease in mucosal somatostatin cells. As mentioned above, both NPY and serotonin have

proinflammatory actions, and somatostatin is an anti-inflammatory peptide. The changes in these neurohormonal peptides/amines would cause accelerated gastrointestinal motility and increased intestinal secretion, resulting in diarrhea, which is the cardinal symptom in IBD. As a feedback response to the accelerated gastrointestinal motility and increased intestinal secretion, the cell density of PYY increases while that of PP decreases. These observations indicate that NPY should be a treatment target for the inflammation that occurs in IBD, which is also supported by the results obtained in DSS-induced colitis in rodents (Hassani et al. 2005; Pang et al. 2010). Administering NPY antisense oligodeoxynucleotides to rats with DSS-induced colitis improves the inflammation and decreases the levels of NPY and TNFα and the expressions of p-Akt and p-NFκB (Pang et al. 2010). The DSS-induced colitis was clinically attenuated in mice with a genetically deficient NPY Y_1 receptor and in those administered with intraperitoneal Y_1 receptor antagonist (Hassani et al. 2005). These data suggest that a Y_1 receptor antagonist should be used to treat IBD. However, since the Y_1 receptor is involved in many biological processes and its administration may interfere with other important biological functions (Balasubramaniam 1997; Hassani et al. 2005; Pang et al. 2010), it might be preferable to consider using a Y_2 receptor antagonist instead.

6. Conclusion

The levels of all members of the NPY peptide family are abnormal in both patients with IBD and animal models of human IBD. These neurohormones appear to play a role in the pathophysiology of IBD by interacting and integrating with other gut neurohormonal peptides/amines. The primary changes seen in IBD appear to be related to NPY and are attributable to an interaction with immune cells during the inflammatory process. On the other hand, changes in PYY and PP appear to be secondary to changes in other gut neurohormonal peptides such as NPY, serotonin, and somatostatin. Therefore, NPY appears to be a key member of the NPY family during the inflammatory process in IBD, indicating the potential of NPY antagonists in therapies for ameliorating the inflammation in IBD.

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