Gastrointestinal neuroendocrine peptides/amines in inflammatory bowel disease

Magdy El-Salhy, Tefera Solomon, Trygve Hausken, Odd Helge Gilja, Jan Gunnar Hatlebakk

Abstract

Inflammatory bowel disease (IBD) is a chronic recurrent condition whose etiology is unknown, and it includes ulcerative colitis, Crohn's disease, and microscopic colitis. These three diseases differ in clinical manifestations, courses, and prognoses. IBD reduces the patients' quality of life and is an economic burden to both the patients and society. Interactions between the gastrointestinal (GI) neuroendocrine peptides/amines (NEPA) and the immune system are believed to play an important role in the pathophysiology of IBD. Moreover, the interaction between GI NEPA and intestinal microbiota appears to play also a pivotal role in the pathophysiology of IBD. This review summarizes the available data on GI NEPA in IBD, and speculates on their possible role in the pathophysiology and the potential use of this information when developing treatments. GI NEPA serotonin, the neuropeptide Y family, and substance P are proinflammatory, while the chromogranin/secretogranin family, vasoactive intestinal peptide, somatostatin, and ghrelin are anti-inflammatory. Several innate and adaptive immune cells express these NEPA and/or have receptors to them. The GI NEPA are affected in patients with IBD and in animal models of human IBD. The GI NEPA are potentially useful for the diagnosis and follow-up of the activity of IBD, and are candidate targets for treatments of this disease.
**Key words:** Enteric nervous system; Enteroeendocrine cells; Immune cells; Inflammatory bowel disease; Musashi-1; Neurogenin 3; Stem cells

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Approximately 80% of the body immune cells (IC) are localized in the gastrointestinal (GI) tract close to the GI neuroendocrine regulatory system (NES). Many IC express GI neuroendocrine peptides/amines (NEPA) and possess receptors to several NEPA. Several GI NEPA are abnormal during active inflammatory bowel disease (IBD) in both patients and animal models of IBD. The changes in the GI NEPA are correlated with those of the IC during the inflammatory process. Studying the interactions between the GI NES and the immune system in IBD may improve our understanding of the pathophysiology of IBD and provide us with new tools for treatment.

El-Salhy M, Solomon T, Hausken T, Gilja OH, Hatlebakk JG. Gastrointestinal neuroendocrine peptides/amines in inflammatory bowel disease. World J Gastroenterol. 2017; 23(28): 5068-5085

Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i28/5068.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i28.5068

**INTRODUCTION**

Inflammatory bowel disease (IBD) is a lifelong recurrent disorder that comprises three diseases: ulcerative colitis (UC), Crohn’s disease (CD), and microscopic colitis (MC). These three diseases have different clinical manifestations, courses, and prognoses[1-3]. Whereas the onset of UC and CD occurs mostly at a young age, MC onset occurs in old age[4,5]. In UC and CD, the activity of the disease varies considerably between patients, from frequent relapses, persistent active disease, to several years of complete remission[4], whereas all MC patients exhibit chronic active disease[6,9]. The inflammation in CD is transmural, in UC it is superficial, and in MC it is in the form of the mucosal and submucosal infiltration of immune cells (IC). CD can arise at any part of the gastrointestinal (GI) tract, while UC and MC affect the recto-colonic mucosa[6,9]. In contrast to UC and CD, spontaneous symptomatic remission occurs in 59%-93% of MC patients[10,11].

IBD diminishes the quality of life considerably and represents an economic problem to both the patients themselves and society[4,9]. The prevalence of IBD amounts to 1.4 million patients in North America and 2.2 million patients in Europe, with 3-20 new cases occurring per 100000 persons annually[12-16]. The prevalence of IBD does not differ among Hispanics, blacks, and Caucasians[17,18]. The incidence of IBD is lower in Asia than in North America and Europe[19-21], but it has been increasing worldwide in recent years[19,21].

The etiology of IBD is not completely understood[9], and the available treatments are not ideal[1-4,22-31]. Typically 70%-80% of the body IC are present in the GI tract in close proximity to the GI neuroendocrine regulatory system (NES)[32,33]. Interactions between the GI neuroendocrine peptides/amines (NEPA) and the immune system have recently been discussed, and it is believed that these interactions play an important part in the pathophysiology of IBD[33-45]. Understanding the role of the GI NEPA in IBD would increase our understanding of the mechanisms underlying the pathophysiology of IBD, and may yield tools for treating these conditions using agonists or antagonists to the GI NEPA[45].

The aim of the present review was to summarize the available data on GI NEA in IBD and to speculate on their possible role in the underlying pathophysiology, and the potential utilization of these peptides/amines in treatments.

**GI NES**

The NES comprises two parts: the GI endocrine cells in the mucosa and the enteric nervous system (ENS) (Figure 1). The GI endocrine cells occur in all segments of the GI tract except for the esophagus[46,47]. These cells lie between the mucosal epithelial cells facing the GI lumen, and they comprise about 1% of all epithelial cells and produce a large number of hormonal peptides/amines[48-56]. The GI endocrine cells are divided into at least 15 different types depending on the hormone they produce[46,49]. Two hormones can be colocalized in the same type of endocrine cell, such as glucagon-like peptide-1 and glucose-stimulated insulinotropic peptide in the small intestine, and peptide YY (PYY) and oxyntomodulin (enteroglucagon) in the distal small and large intestines[57-60]. It has been shown recently that mature GI endocrine cells can express up to seven different hormones[51,52,61-64].

The GI endocrine cells have specialized sensory microvilli that project into the lumen, and they respond to luminal stimuli (mostly nutrients and/or bacteria byproducts) by releasing their hormones into the lamina propria[52,42,66-68]. The cells also possess a basal cytoplasmic process about 70 μm long that is believed to be involved in their paracrine mode of action[86-89]. It has been shown recently that this process exhibits neuronal axon-like characteristics, and it has been named a neuropod[88-91]. The GI endocrine cells also exhibit synaptic vesicles and synthesize presynaptic proteins: synapsin 1, piccolo, bassoon, MUNC13B, RIMS2, latrophilin, and transsynaptic neurexin[88,91-93]. These cells also synthesize transsynaptic neurologin 2 and 3, homer 3, and postsynaptic density 95[93]. Thus, the GI endocrine cells possess the elements necessary for both afferent and efferent synaptic transmission[93].
These data suggest that the GI hormones released in the lamina propria could act locally on close by cells or neurons (paracrine mode), through the circulating blood (endocrine mode), or by afferent and efferent synaptic transmission \(^{94-97}\). The released hormones exert their effects via three modes of action: (1) entering the circulating blood and reaching distant targets (endocrine mode); (2) acting locally on nearby structures (paracrine mode); or (3) via synaptic activity. Reproduced from reference 46 with permission from the authors and the publisher.

Recent observations of GI endocrine cells exhibiting both endocrine and neuron-like characteristics support a long-standing hypothesis about the evolution of the GI NES\(^ {98}\). The absence of mammalian GI hormonal peptides in the gut of invertebrates, and the occurrence of these peptides in the central nervous system (CNS)\(^ {99-101}\) resulted in the hypothesis that the GI endocrine cells of vertebrates initiated in the nervous system of a common ancestor of invertebrates and vertebrates and then moved during a later stage of evolution into the gut as endocrine cells\(^ {98}\).

The ENS is an independent nervous system within the GI tract that consists of two plexi: one located in the submucosa (the submucosal plexus) and one situated between the longitudinal and circular muscle layers (the myenteric plexus)\(^ {102-104}\). The neurons of the ENS (about 100 million) are modulated by afferent and efferent nerve fibers from the CNS and the autonomic nervous system\(^ {102-104}\). The GI endocrine cells integrate and interact with each other and with the ENS\(^ {105}\).

**INTERACTION BETWEEN THE GI NES AND INTESTINAL MICROBIOTA**

It has long been believed that IBD is caused bacterial infection, and this belief lead to the introduction of salazopyrine (5-aminosalicylic acid-sulfapyridine) for the treat of IBD\(^ {106,107}\). However, A specific microbe(s) could not be identified as the cause of IBD\(^ {106}\). Recent studies have shown, however, that intestinal microbiota plays an important role in the pathophysiology of IBD\(^ {106}\). Thus, low intestinal microbiome diversity and dysbiosis appear to be important factors in the pathophysiology of IBD\(^ {106}\). The short-chain fatty
acids produced upon fermentation of dietary fibers in the large intestine affect both the immune system and the NES. Butyrate is one of these short-chain fatty acids\(^{108,109}\). Butyrate suppresses large intestinal inflammation by inducing T-cell apoptosis, and by suppressing IFN-\(\gamma\)-mediated inflammation\(^{110-112}\). The short-chain fatty acids affect several GI peptides, such as PYY and glucagon-like peptide-1\(^{105,113-115}\). Furthermore butyrate has been found to affect neurons of the ENS\(^{113,116}\).

**INTERACTIONS BETWEEN THE GI NES AND THE IMMUNE SYSTEM**

Several NEPA of the GI NES have been shown to interact with the immune system, including members of the chromogranin/secretogranin family, serotonin, vasoactive intestinal peptide (VIP), members of the neuropeptide Y (NPY) family, substance P, somatostatin, and ghrelin.

**Chromogranin/secretogranin family**

All of the GI endocrine cell types produce members of the granins family (including chromogranins A and B) that are co-stored and co-released from the GI endocrine cells\(^{34,117-120}\). Chromogranin A (CgA) occurs in all GI tract endocrine cell types\(^{121-124}\). CgA-derived peptides decrease interleukin (IL)-16 and IL-5 release, and hence decrease the density of lymphocytes at inflammatory sites and thus the proinflammatory action of lymphocytes and monocytes\(^{125-127}\). Members of the chromogranin/secretogranin family are believed to exert anti-inflammatory effects.

**Serotonin**

About 95% of the body serotonin occurs in the GI, of which only 10% occurs in the neurons of the ENS and the rest in the enterochromaffin cells\(^{34,128}\). Serotonin is believed to play a pivotal role in intestinal inflammation\(^{34,36,40,125,126,130}\). Mast cells, macrophages/monocytes, and T cells are capable of producing serotonin\(^{131}\). Serotonin receptors occur in numerous innate IC such as neutrophils, eosinophils, monocytes, macrophages, dendritic cell, mast cells, and natural killer (NK) cells, and in cells of the adaptive immune system such as lymphocytes\(^{130-132}\). Serotonin promotes the activation of lymphocytes, whose proliferation protects NK cells and T-helper cells, hinders the apoptosis of IC, and endorses the recruitment of T cells\(^{133-137}\). The number of intestinal serotonin cells is decreased in knockout mice lacking T-lymphocyte receptors\(^{125}\). Serotonin cells express IL-13 receptors\(^{138}\). Against this background, serotonin is considered to be a proinflammatory amine during the inflammatory process.

**VIP**

VIP is a 28-amino-acid peptide exhibiting structural similarities with secretin\(^{139}\). VIP is secreted by neurons, endocrine cells, and IC, and it occurs in almost all body organs\(^{140}\). In GI tract, VIP occurs in endocrine cells and neurons of the ENS\(^{141,142}\). VIP is believed to be a major immune-regulating neuropeptide that plays an important role in inflammatory disorders, and is considered to be a natural anti-inflammatory agent\(^{142,143}\).

Both CD4 and CD8 T cells produce VIP, especially following antigen stimulation\(^{144,145}\). The VIP receptor VPAC1 occurs in lymphocytes, macrophages, monocytes, dendritic cells, microglia, and mast cells\(^{146,147}\). VIP inhibits the production of proinflammatory cytokines such as tumor necrosis factor \(\alpha\) (TNF\(\alpha\)), IL-6, IL-12, iNOS, and promotes the production anti-inflammatory cytokines such as IL-10\(^{148-153}\). VIP also inhibits the transcription factors AP-1, nuclear factor-\(\kappa\)B (NF-\(\kappa\)B), CREB, and IRF-1\(^{142,147,155,156}\), and impairs the acquisition of the macrophage proinflammatory polarization profile\(^{152}\).

**NPY family**

The NPY family includes three neuroendocrine peptides that act as hormones and/or neurotransmitters/neuromodulators: NPY, PYY, and pancreatic polypeptide (PP)\(^{156-160}\). These peptides consists of 36-amino-acid residues and are structurally related\(^{161}\). NPY is expressed in the neurons of the CNS and NES\(^{158,159,162}\). PYY and PP are expressed by endocrine cells of the ileum, colon, and rectum\(^{163-165}\). PP occurs also in endocrine cells in pancreatic islets of Langerhans\(^{166}\). NPY and PYY exert similar biological effects\(^{160,164,165}\), and they act through binding to receptors Y\(_1\) and Y\(_2\)\(^{166-169}\). T lymphocytes, macrophages, and dendritic cells produce NPY during inflammation\(^{170}\). NPY Y\(_1\)/Y\(_2\) receptors are localized on IC\(^{171,172}\) and the binding of NPY to these receptors induces the release of proinflammatory cytokines and nitric oxide from macrophages, neutrophils, and lymphocytes\(^{171,173}\). NPY therefore exerts proinflammatory effects in the presence of an inflammatory process. The role of PYY and PP in inflammation is not yet known.

**Substance P**

Substance P is a member of the tachykinin family and substance P nerve fibers are widely distributed in the GI wall. Substance P is localized in enteric efferent neurons\(^{174-176}\) and is expressed by several IC including T cells, macrophages, dendritic cells, and eosinophil cells\(^{177-182}\). It also plays an important role in the migration of innate IC such as neutrophils and macrophages, and of adaptive IC such as T lymphocytes\(^{183-190}\). Furthermore, substance P regulates the proliferation of lymphocytes and modulates the activities of innate and adaptive IC\(^{179,183,191}\). Substance P is therefore considered to be one of the main proinflammatory mediators in the GI tract.

**Somatostatin**

The GI tract and the pancreas contain most of the body...
somatostatin\(^{[192,193]}\). About 90% of GI somatostatin is localized in GI endocrine cells, and the remaining 10% is in neurons of the ENS\(^{[194]}\). Somatostatin binds to five membrane G-protein-coupled receptor subtypes (SSTR 1-5)\(^{[195]}\). Several innate and adaptive IC such as monocytes/macrophages, B lymphocytes, T lymphocytes, and dendritic cells expressed these receptors\(^{[195-204]}\). Somatostatin stimulates B-lymphoblast proliferation with the enhancement of immunoglobulin formation\(^{[205]}\), inhibits T lymphocytes and granulocyte proliferation, and reduces proinflammatory cytokines such as IFN-\(\gamma\)\(^{[194,196,206-213]}\). Somatostatin is considered to be an anti-inflammatory peptide\(^{[37,214,215]}\).

Ghrelin

Ghrelin is a peptide composed of 28-amino-acid that occurs mostly in X/A endocrine cells in the oxyntic mucosa of the stomach\(^{[42,50,216-221]}\). Ghrelin performs several functions, including controlling food intake, energy homeostasis, and GI motility\(^{[217,218,221-224]}\). It also mediates the immune response and inflammation\(^{[146,225-227]}\). The anti-inflammatory properties of ghrelin are due to it modulating the secretion of pro- and anti-inflammatory cytokines from LPS-stimulated macrophages\(^{[225]}\).

NES NEPA IN IBD

**NES abnormalities IN IBD**

Changes in the ENS in IBD such as an increase in the number of enteric neurons, and altered neurotransmitter synthesis and release have been described\(^{[228-237]}\). Similarly, the density of the GI endocrine cells, the proportions of different endocrine cell types, and the release of GI NEPA are affected in both IBD patients and animal models of human IBD.

**Chromogranin/secretogranin family:** The circulating level of CgA is elevated in IBD patients and is reduced following treatment with certain biological agents\(^{[196,238-241]}\). Patients with IBD exhibit elevated concentrations of fecal CgA and secretogranins\(^{[242,243]}\). The CgA cell density is increased in patients with IBD, and in animal models of human UC and CD, with the exception of trinitrobenzene sulfonic acid (TNBS)-induced colitis\(^{[9,117,244-248]}\) (Figure 3). The administration of the proinflammatory cytokines IFN-\(\gamma\) and TNF-\(\alpha\) and the induction of colitis by dextran sodium sulfate (DSS) in mice were found to increase the number of CgA cells\(^{[249]}\).

**Serotonin:** The density of colonic serotonin cells is elevated in patients with UC, CD, and lymphocytic colitis\(^{[117,250]}\) (Figure 4). The serotonin cell density was also increased in an animal model of human UC (TNBS-induced colitis in rats) and in an animal model of human CD (DSS-induced colitis in rats), as well as in other animal models of human UC and CD, and in IL-2-knockout mice\(^{[230,244,245,251,252]}\).

**VIP:** Studies of VIP in patients with IBD have produced conflicting results. The immunohistochemical examination and quantification of tissue extracts from rectal biopsy samples obtained from patients with UC and CD showed an increased number of VIP-positive nerve fibers and an increased VIP concentration in CD but not in UC\(^{[253]}\). Other studies found that the number of VIP-positive nerve fibers was either decreased or unchanged in patients with UC and CD\(^{[245,254,255]}\). These contradictory results for VIP in patients with IBD could be explained by VIP occurring mostly in neurons of the ENS and that analyzing VIP in small mucosal biopsy specimens obtained during an endoscopic examination does not produce reliable results. However, changes in VIP have been found in animal models of human IBD, especially knockout mice\(^{[251]}\). In IL-2 gene-knockout mice, the relative volume density of VIP-positive nerve fibers and the level of VIP in tissue extracts were both decreased\(^{[251]}\).

**NPY family:** The density of NPY enteric neurons increased as well as hyperplasia of NPY nerve fibers have been observed in mice with colitis induced either by DSS or streptomycin-pretreated Salmonella typhimurium\(^{[256,257]}\). The PYY cell density is increased in patients with UC and lymphocytic colitis as well
as in colitis induced by DSS in rats and in IL-2 gene-knockout mice\cite{117,245,250,251}. The PYY cell density is decreased in CD, with this change being correlated positively with the increased disease severity\cite{117}. Similarly, the density of PYY cells was reduced in an animal model of human CD, namely TNBS-induced colitis in rats\cite{244}. The robust positive correlation between the PYY cells and IC found in colitis induced either by DSS, or TNBS in rats is suggestive of an interaction between PYY cells and the IC\cite{244,245}. It is noteworthy that PYY and oxyntomodulin (entero-glucagon) are produced from the same endocrine cell (L cells)\cite{57}. Whereas the density of oxyntomodulin-containing cells is increased in patients with CD and in both DSS- and TNBS-induced colitis, and in IL-2 gene-knockout mice, it is unchanged in patients with UC\cite{118,244,251,258}. The PP cell density is decreased in patients with CD and in colitis induced by either DSS, or TNBS in rats\cite{117,245,248}.

**Substance P:** The levels of substance P are increased in tissue extracts from the colon and in the rectum of patients with UC and CD, and were correlated with disease activity\cite{253,259-261}. The density of nerve fibers immunoreactive to substance P is decreased in the colon of UC patients\cite{162}. The density of substance-P-immunoreactive fibers has been reported to be both increased\cite{253,262} and unchanged\cite{162} in the colon of CD patients. The concentration of substance P in the colon of IL-2-knockout mice is decreased, while substance-P-immunoreactive cells were unchanged\cite{251}.

**Somatostatin:** The number of somatostatin cells is decreased in the colon of patients with IBD, and in animal models of human IBD, except for TNBS-induced colitis where it is increased\cite{245,263-265} (Figure 5).

**Ghrelin:** The circulating levels of ghrelin are elevated in patients with IBD with active inflammation\cite{266,267}. Moreover, circulating ghrelin levels in UC and CD patients are correlated with TNF\textsubscript{\alpha}, C-reactive protein, the erythrocyte sedimentation rate, and fibrinogen, and negatively correlated with nutritional status parameters\cite{42,228,268,269}.

### Possible mechanisms underlying NES abnormalities in IBD

The mechanisms underlying the changes in ENS during inflammation in IBD remain unclear. However, recent studies have shed some light on the possible mechanisms of the inflammation-induced changes in the GI endocrine cells in IBD\cite{258,270}.

Whereas changes in GI endocrine cells do occur in UC, CD, lymphocytic colitis, and animal models of human IBD, the nature of these changes differ between the different IBDs and animal models.
July 28, 2017 | Volume 23 | Issue 28 | WJG | www.wjgnet.com

El-Salhy M et al. GI neuroendocrine peptides/amines and IBD

Figure 6  Proinflammatory substances such as cytokines may act on the intestinal stem cells and increase their clonogenic and differentiation progeny so that the density of intestinal endocrine cells increases during active inflammation.

Abnormal stem cell clonogenic and differentiation activities: Each intestinal crypt contains four to six stem cells that either divide into identical new stem cells (clonogenic) or differentiate into all types of epithelial cells through a series of progenitors. This differentiation into epithelial cells includes the secretory and absorptive lineages. The secretory lineage gives rise to endocrine, goblet, and Paneth cells. The absorptive lineage results to absorptive enterocytes. In rats with TNBS-induced colitis, which is an animal model of human CD, the colonic density of Musashi-1 (Musi-1) immunoreactive cells was found to be reduced. In contrast, the colonic density of Musi-1 cells was unaffected in rats with DSS-induced colitis, which is an animal model of human UC. Musi-1 is located in both intestinal stem cells and early progenitors. These observations indicate that the clonogenic activity of stem cells is affected in an animal model of CD but not in one of UC. This is probably due to the inflammation associated with CD being deep while that associated with UC being superficial.

In rats with both TNBS- and DSS-induced colitis, the colonic Math-1 cell density was found to be unaffected. Math-1 occurs early progenitor in the secretory lineage, and mutant (Math-1-/-) mice have no secretory cells.

The colonic neurogenin 3 (Neurog3) cell density is reduced in rats with TNBS-induced colitis, while it is increased in rats with DSS-induced colitis. Neurog3 is localized in an early progenitor belonging to the secretory lineage, which contributes to the differentiation into endocrine cells. Transgenic mice (Neurog3+/-) do not have enteroendocrine cells, but normal densities of goblet and Paneth cells. Similar to Neurog3, the colonic NeuroD1 cell density is decreased in rats with TNBS-induced colitis while it is increased in rats with DSS-induced colitis. NeuroD1 is located in progenitors originated from Neurog3 progenitors. Mice deficient in NeuroD1 lacks certain types of enteroendocrine cells. These findings show that the differentiation progeny toward endocrine cells is affected in animal models of human IBD.

Switching the expression of NEPA on and off:

As mentioned above, mature GI endocrine cells can express up to seven different hormones. It seems that the changes in the proportion of GI endocrine cells during inflammation occur via switching off the synthesis of a neuroendocrine peptide/amine and switching on the synthesis of another. Such a phenomenon has been reported in rats with TNBS-induced colitis (Figure 8).

Hypothesis: It may be speculated that during the inflammation that occurs in active IBD, the IC produce proinflammatory cytokines and other substances that affect the GI stem cells and mature endocrine cells. This will induce abnormal clonogenic and differentiation activities of stem cells. Moreover, the mature endocrine cells switch off the expression of a neuroendocrine peptide/amine and switching on the synthesis of another hormone. This would result in changes in the total density of endocrine cells and in the proportion of different endocrine cell types. NPA produced by the altered endocrine cells would in return affect the IC via their NPA receptors (Figure 9).

CLINICAL IMPLICATIONS

The changes in the intestinal NES associated with inflammation in IBD patients are believed to be useful tools for the diagnosis and follow-up of disease activity. Furthermore, the GI NEA could be candidate targets of IBD treatments. Thus, agonists to anti-inflammatory NEPA and antagonists to proinflammatory NEPA can be used not only for their pharmacological effects but also to correct a pre-existing imbalance in GI NEPA caused by inflammation.

Diagnosis

The colonic CgA cell density has been shown to be a
A good biomarker for diagnosing lymphocytic colitis, with a high sensitivity and specificity\(^9\). The blood and fecal levels of CgA and secretogranins have been proposed for the diagnosis and follow-up of the disease activity in IBD\(^{[56,238-243]}\). Treatment with CgA-derived peptides of mice with DSS-induced colitis decreases the disease activity index, macroscopic and histology scores, and the colonic levels of IL-1\(\beta\), IL-6, and TNF\(\alpha\)\(^{[34]}\). Antagonists of serotonin receptors 5-HTR3 and 5-HTR7 such as tropisetron, granisetron, ondansetron, ramosetron, and SB-269970 have shown anti-inflammatory effects in animal models of human IBD\(^{[292-300]}\). These serotonin receptor antagonists act via reducing the synthesis of proinflammatory cytokines IL-1, IL-6, and TNF\(\alpha\). The usefulness of selective inhibition of mucosal serotonin by these receptor antagonists in the clinical treatment of IBD remains to be determined\(^{[301]}\).

VIP is believed to be a potential agent for treating IBD since it targets both the innate and adaptive immune responses and inhibits the secretion of numerous proinflammatory cytokines via its actions on AP-1 and NF\(\kappa\)B\(^{[142]}\). Administering VIP reduced inflammation in TNBS-induced colitis in mice\(^{[142]}\), and it has been used successfully in the clinic as an inhalator for treating pulmonary hypertension and sarcoidosis\(^{[142]}\). However, delivering VIP is problematic since it is degraded rapidly in the blood circulation (with a half-life of only 1-2 min) and systemic administration causes both cardiovascular and intestinal side effects\(^{[140,302,303]}\).

NPY occupies a key position during the inflammatory process in IBD, and NPY antagonists could be potentially useful in treatments for the inflammation in IBD\(^{[43]}\). This suggestion is supported by observations made in animal models of UC, namely DSS-induced colitis in rats\(^{[303,304]}\). Treatment with NPY...

**Figure 7** During the inflammatory process, several proinflammatory substances may act on the mature enteroendocrine cells so that they switch off the expression of a certain enteroendocrine peptides/amines and switch on the expression of another enteroendocrine peptides/amines.

**Figure 8** Colonic densities of (A) peptide YY-positive cells and (B) oxyntomodulin (enteroglucagon)-positive cells in control rats, in rats with trinitrobenzene sulfonic acid (TNBS)-induced colitis, and in rats with TNBS-induced colitis treated with 3-[(dodecylthiocarbonyl)-methyl]-glutarimide (DTCM-G, an activator protein-1 inhibitor) and dehydroxymethylepoxyquinomicin (DHMEQ, a nuclear factor-\(\kappa\)B inhibitor). Densities of PYY-positive and oxyntomodulin-positive cells in each rat of the TNBS group (C), and their correlation (D). \(r = 0.7, P = 0.04\).
El-Salhy M et al. GI neuroendocrine peptides/amines and IBD

**REFERENCES**

1. Prantera C, Marconi S. Glucocorticosteroids in the treatment of inflammatory bowel disease and approaches to minimizing systemic activity. *Therap Adv Gastroenterol* 2013; 6: 137-156 [PMID: 23503968 DOI: 10.1177/1756283X12473675]

2. Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002; 347: 417-429 [PMID: 12167685 DOI: 10.1056/NEJMra020831]

3. Podolsky DK. The current future understanding of inflammatory bowel disease. *Best Pract Res Clin Gastroenterol* 2002; 16: 933-943 [PMID: 12473299]

4. Carter MJ, Lobo AJ, Travis SP. IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004; 53 Suppl 5: V1-V16 [PMID: 15306569 DOI: 10.1136/gut.2004.03372]

5. Rasmussen MA, Munk LK. Systematic review: are lymphocytic colitis and collagenous colitis two subtypes of the same disease - microscopic colitis? *Aliment Pharmacol Ther* 2012; 36: 79-90 [PMID: 22670660 DOI: 10.1111/j.1365-2636.2012.05166.x]

6. Danese S, Fiocchi C. Etiopathogenesis of inflammatory bowel diseases. *World J Gastroenterol* 2006; 12: 4807-4812 [PMID: 16937461 DOI: 10.3748/wjg.v12.4807]

7. Nunes T, Fiorino G, Danese S, Sans M. Familial aggregation in inflammatory bowel disease: is it genes or environment? *World J Gastroenterol* 2011; 17: 2715-2722 [PMID: 21734779 DOI: 10.3748/wjg.v17.2715]

8. El-Salhy M, Gundersen D, Hatlebakk JG, Hausken T. Clinical presentation, diagnosis, pathogenesis and treatment options for lymphocytic colitis (Review). *J Int Med Res* 2013; 41: 520-532 [PMID: 23695201 DOI: 10.3892/jim.2013.1385]

9. El-Salhy M, Gundersen D, Hatlebakk JG, Hausken T. Chromogranin A cell density as a diagnostic marker for lymphocytic colitis. *Dig Dis Sci* 2012; 57: 3154-3159 [PMID: 22699394 DOI: 10.1007/s10620-012-2249-6]

10. Baert F, Wouters K, D’Haens G, Hoang P, Naegels S, D’Hegere F, Holvoet J, Louis E, Devos M, Geboes K. Lymphocytic colitis: a distinct clinical entity? A clinicopathological confrontation of lymphocytic and collagenous colitis. *Gut* 1999; 45: 375-381 [PMID: 10446105]

11. Mullhaupt B, Güller U, Anabitarte M, Güller R, Fried M. Lymphocytic colitis: clinical presentation and long term course. *Gut* 1998; 43: 629-633 [PMID: 9824342]

12. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; 126: 1504-1517 [PMID: 15168363]

13. Loftus EV Jr, Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; 31: 1-20 [PMID: 12122726]

14. Selch M, Elson CO. Experimental inflammatory bowel disease:
Sundler F, Christensen N, Wierup N, Olsen JV, Holst JJ, Zigman JM, Poulsen SS, Schwartz TW. A major lineage of enteroglucagon cells coexpresses CCK, secretin, GIP, GLP-1, PYY, and neurotensin but not somatostatin. Endocrinology 2012; 153: 5782-5795 [PMID: 22066014 DOI: 10.1210/endo.2012-1595]

52 Engelstoft MS, Egerod KL, Lund ML, Schwartz TW. Enteroglucagon cell types revisited. Curr Opin Pharmacol 2013; 13: 912-921 [PMID: 24140256 DOI: 10.1016/j.coph.2013.09.018]

53 Schonhoff SE, Giel-Moloney M, Leiber AB. Minireview: Development and differentiation of gut endocrine cells. Endocrinology 2004; 145: 2639-2644 [PMID: 15044355 DOI: 10.1210/endo.2004-0051]

54 Shulkes A. Gastrointestinal hormones: from basic science to a clinical perspective. Aust N Z J Surg 1990; 60: 575-578 [PMID: 2202281]

55 Socia E, Fiocca R, Rindi G, Villani L, Cornaggia M, Capella C. The pathology of the gastrointestinal endocrine system. Endocrinol Metab Clin North Am 1993; 22: 795-821 [PMID: 8120073]

56 Zissimopoulos A, Vradelis S, Konialis M, Chadolias D, Bampali A, Constantinidis T, Efremidou E, Kouklakis G. Chromogranin A as a biomarker of disease activity and biologic therapy in inflammatory bowel disease: a prospective observational study. Scand J Gastroenterol 2014; 49: 942-949 [PMID: 24879113 DOI: 10.3109/00365521.2014.920910]

57 Spangéus A, Forsgren S, el-Salhy M. Does diabetic state affect co-localization of peptide YY and enteroglucagon in colonic endocrine cells? Histol Histopathol 2000; 15: 37-41 [PMID: 10668193]

58 Pyarokhil AH, Ishihara M, Sasaki M, Kitamura N. The developmental plasticity of colocalization pattern of peptide YY and glucagon-like peptide-1 in the endocrine cells of bovine rectum. Biomed Res 2012; 33: 35-38 [PMID: 22361884]

59 Mortensen K, Christensen LL, Holst JJ, Orskov C. GLP-1 and GIP are colocalized in a subset of endocrine cells in the small intestine. Regul Pept 2003; 114: 189-196 [PMID: 12832109]

60 el-Salhy M, Wilander E, Grimalius L. Immunocytochemical localization of gastric inhibitory peptide (GIP) in the human fetal pancreas. Ups J Med Sci 1982; 87: 81-85 [PMID: 6750891]

61 Ghia JE, Li N, Wang H, Collins M, Deng Y, El-Sharkawy RT, Shibata M, Vradelis S, Konialis M, Chadolias D, Bampali A, Anouar Y. Chromogranin A promotes peptide hormone sorting to mobile granules in constitutively and regulated secreting cells: role of conserved N- and C-terminal peptides. J Biol Chem 2009; 284: 12420-12431 [PMID: 19719393 DOI: 10.1074/jbc.M805670200]

62 Shooshhtarizadeh P, Zhang D, Chich JF, Gasièr C, Schneider F, Haikel Y, Assim D, Metz-Boutigue MH. The antimicrobial peptides derived from chromogranin/secretogranin family, new actors of innate immunity. Regul Pept 2010; 165: 102-110 [PMID: 19932135 DOI: 10.1016/j.regpep.2009.11.014]

63 Reber SO, Obermeier F, Straub RH, Falk W, Neumann ID. Chronic intermittent psychosocial stress (social defeat/overcrowding) in mice increases the severity of an acute DSS-induced colitis and impairs regeneration. Endocrinology 2006; 147: 4968-4976 [PMID: 16794011 DOI: 10.1210/en.2006-0347]

64 Milde AM, Murison R. A study of the effects of restraint stress on colitis induced by dextran sulphate sodium in singly housed rats. Integr Physiol Behav Sci 2002; 37: 140-150 [PMID: 12186308]

65 Hassani H, Lucas G, Rozell B, Emfors P. Attenuation of acute experimental colitis by preventing NPY Y1 receptor signaling. Am J Physiol Gastrointest Liver Physiol 2005; 288: G550-G556 [PMID: 15499082 DOI: 10.1152/ajpgi.00182.2004]

66 Cani PD, Everard A, D supervisor. Gut microbe, enterohormone, endocrine functions and metabolism. Curr Opin Pharmacol 2013; 13: 935-940 [PMID: 24075718 DOI: 10.1016/j.coph.2013.09.008]

67 Cani PD, Hoste S, Guiot Y, Delzenne NM. Dietary non-digestible carbohydrates promote L-cell differentiation in the proximal colon of rats. Br J Nutr 2007; 98: 32-37 [PMID: 17367575 DOI: 10.1017/s0007114506791648]

68 Pettito JM, Huang Z, McCarthy DB. Molecular cloning of NPY-Y1 receptor cDNA from rat splenic lymphocytes: evidence of low levels of mRNA expression and [125I]NPY binding sites. J Neuroimmunol 1994; 54: 81-86 [PMID: 7929806]

69 de la Fuente M, Bernez D, Montanez A, Hernandez A. Stimulation of murine peritoneal macrophage functions by neuropeptide Y and peptide YY. Involvement of protein kinase C. C. Immunology 1993; 80: 259-265 [PMID: 8262534]

70 Shibata M, Hisajima T, Nakano M, Goris RC, Funakoshi K. Morphological relationships between peptidergic nerve fibers and immunoglobulin A-producing lymphocytes in the mouse intestine. Brain Behav Immun 2008; 22: 158-166 [PMID: 17931829 DOI: 10.1016/j.bbi.2007.08.013]

71 Painisp E, Herzog H, Sperk G, Holzer P. Sex-dependent control of murine emotional-affective behaviour in health and colitis by peptide YY and neuropeptide Y. Br J Pharmacol 2011; 163: 1302-1314 [PMID: 21410462 DOI: 10.1111/j.1476-5381.2011.01326.x]

72 Raybould HE. Nutrient sensing in the gastrointestinal tract: possible role for nutrient transporters. J Physiol Biochem 2008; 64: 349-356 [PMID: 19391461]
Bugs, genes, fatty acids, and serotonin: neurohormonal mechanisms. Camilleri M. Unraveling inflammatory bowel disease? F1000Res 2015; 4: 2783-2800 [PMID: 22562678 DOI: 10.12688/f1000research.6456.1]

Kauntz J, Nayyar P. Bugs, genes, fatty acids, and serotonin: Unraveling inflammatory bowel disease? F1000Res 2015; 4: 2783-2800 [PMID: 22562678 DOI: 10.12688/f1000research.6456.1]

Kirsner JB. Historical aspects of inflammatory bowel disease. J Clin Gastroenterol 1988; 10: 286-297 [PMID: 2907864]

Eswarzan S, Mui J, Chey WD. Fiber and functional gastrointestinal disorders. Am J Gastroenterol 2013; 108: 718-727 [PMID: 23545709 DOI: 10.1038/ajg.2013.63]

Chutkan R, Fahey G, Wright WL, McRorie J. Viscous versus nonviscous soluble fiber supplements: mechanisms and evidence for fiber-specific health benefits. J Acad Nutr Diet 2012; 24: 476-487 [PMID: 22845031 DOI: 10.1111/j.1754-7992.2012.07588.x]

Zimmerman MA, Singh N, Martin PM, Thangaraju M, Ganapathy V, Waller JL, Shi H, Robertson KD, Munn DH, Liu K. Butyrate suppresses colonic inflammation through HDAC1-dependent fasting upregulation and Fas-mediated apoptosis of T cells. Am J Physiol Gastrointest Liver Physiol 2012; 302: G1405-G1415 [PMID: 22517765 DOI: 10.1152/ajpgi.00543.2011]

Klapper L, Huang J, Sasaki T, Shirasawa S, Augenlicht L. Inhibition of interferon gamma signaling by the short chain fatty acid butyrate. Mol Cancer Res 2003; 1: 855-862 [PMID: 14517348]

Stempell M, Keding M, Augenlicht L, Klapper L. Essential role of the JAK/STAT1 signaling pathway in the expression of inducible nitric-oxide synthase in intestinal epithelial cells and its regulation by butyrate. J Biol Chem 2007; 282: 9797-9804 [PMID: 17251186 DOI: 10.1074/jbc.M609426200]

Holzer P, Farzi A. Neuropeptides and the microbiota-gut-brain axis. Adv Exp Med Biol 2014; 815: 195-219 [PMID: 24997035 DOI: 10.1007/978-1-4939-0897-4_9]

Everard A, Cani PD. Gut microbiota and GLP-1. Rev Endocr Metab Disord 2014; 15: 189-196 [PMID: 24789701 DOI: 10.1007/s11514-014-9288-6]

Arota T, Loo RL, Anastasovska J, Gibson GR, Tuohy KM, Sharma RK, Swann JR, Deaville ER, Sleeth ML, Thomas EL, Holmes E, Bell JD, Frost G. Differential effects of two fermentable carbohydrates on central appetite regulation and body composition. PLoS One 2012; 7: e43263 [PMID: 22952566 DOI: 10.1371/journal.pone.0043263]

Soret R, Chevalier J, De Coppet P, Pouppeau G, Derkinderen P, Segain JP, Neullist M. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. Gastroenterology 2010; 138: 1772-1782 [PMID: 20152836 DOI: 10.1053/j.gastro.2010.01.053]

El-Salhy M, Danielsson A, Stenling R, Grimelius L. Colonic endocrine cells in inflammatory bowel disease. J Intern Med 1997; 242: 413-419 [PMID: 9408072]

Buffa R, Marré P, Gini A, Salvadoro M. Chromogranins A and B and secretogranin II in hormonally identified endocrine cells of the gut and the pancreas. Basic Appl Histochem 1988; 32: 471-484 [PMID: 3223865]

D’Amico MA, Ohinawas I, Bizzicupo P, Manzoli L, Di Baldassarre A. Biological function and clinical relevance of chromogranin A and derived peptides. Endocr Connect 2014; 3: R45-R54 [PMID: 24671122 DOI: 10.1530/EC-14-0027]

Helle KB. Regulatory peptides from chromogranin A and secretogranin II: putative modulators of cells and tissues involved in inflammatory conditions. Regul Pept 2010; 165: 45-51 [PMID: 19800929 DOI: 10.1016/j.regpep.2009.09.009]

El-Salhy M, Lomboldt-Beck B, Hausken T. Chromogranin A as a possible tool in the diagnosis of irritable bowel syndrome. Scand J Gastroenterol 2010; 45: 1435-1439 [PMID: 20602602 DOI: 10.3109/03002249.2011.561878]
12 Taupenot L, Harper KL, O’Connor DT. The chromogranin-secretogranin family. N Engl J Med 2003; 348: 1134-1149 [PMID: 12646671 DOI: 10.1056/NEJMoa021405]

123 Wiedemann B, Hattner WB. Synaptophysin and chromogranins-secretogranins—widespread constituents of distinct types of neuroendocrine vesicles and new tools in tumor diagnosis. Virchows Arch B Cell Pathol Incl Mol Pathol 1989; 58: 95-121 [PMID: 2575822]

124 Defos LJ. Chromogranin A: its role in endocrine function and as an endocrine and neuroendocrine tumor marker. Endocr Rev 1991; 12: 181-187 [PMID: 2070778]

125 Spiller R. Secretion and GI clinical disorders. Neuropharmacology 2008; 55: 1072-1080 [PMID: 18687345 DOI: 10.1016/j.neuropharm.2008.07.016]

126 Egger M, Beer AG, Theuril M, Schgoer W, Hotter B, Tatarczyk T, Vasilijevic D, Frauscher S, Marksteiner J, Patsch JR, Schratzerberger P, Djanani AM, Mahata SK, Kirchmair R. Monocyte migration: a novel effect and signaling pathways of catestatin. J Immunol 2009; 184: 101-111 [PMID: 18834877 DOI: 10.1067/j.ji.2008.09.016]

127 Feistritzer C, Mosheiner BA, Colleselli D, Wiedermann CJ, Kahler CM. Effects of the peptide secretoneurin on natural killer cell migration and cytokine release. Regul Pept 2005; 126: 195-201 [PMID: 15664667 DOI: 10.1016/j.regpep.2004.10.001]

128 Gershon MD. Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology 2007; 132: 397-414 [PMID: 17241888 DOI: 10.1016/j.gastro.2006.11.002]

129 Shahbakhshani B, Foroostan M, Merat S, Akbari MR, Nasserimoghadam H, Vahedi H, Malekzadeh R. Coeliac disease presenting with symptoms of irritable bowel syndrome. J Gastroenterol Hepatol 2010; 25: 1947-1955 [PMID: 17429435 DOI: 10.1111/j.1440-1746.2010.06010.x]

130 Rettenmayer J, Martinez MC, Delgado M, Garrido E, Gomariz RP. VIP impairs acquisition of the macrophage proinflammatory polarization profile. J Leukoc Biol 2007; 81: 599-606 [PMID: 17108054 DOI: 10.1189/jlb.0906544]

131 Stefulj J, Cinc-Sain L, Schauenstein K, Jernej B. Secretoneurin and immune response: effect of the amine on vitro proliferation of rat lymphocytes. Neuroimmunomodulation 2001; 9: 103-108 [PMID: 11549892]

132 Betten A, Daghren C, Hermodsson S, Hellstrand K. Serotonin protects NK cells against oxidatively induced functional inhibition and apoptosis. J Leukoc Biol 2001; 70: 65-72 [PMID: 11435487]

133 Laberge S, Cuijkshank WW, Beer DJ, Center DM. Secretion of IL-16 (lymphocyte chemoattractant factor) from secretoneurin-stimulated CD8+ T cells in vitro. J Immunol 1996; 156: 310-315 [PMID: 8958478]

134 Soga F, Katoh N, Inoue T, Kishimoto S. Serotonin activates human T cell-mediated immunological control of enterochromaffin cell hyperplasia and 5-hydroxytryptamine production in enteric infection. Gut 2007; 56: 949-957 [PMID: 17303357 DOI: 10.1136/gut.2006.103226]

135 El-Salhy M. Gastrointestinal transit in nonobese diabetic mouse: an animal model of human diabetes type 1. J Diabetes Complications 2001; 15: 277-284 [PMID: 11561557]

136 Henning RJ, Sawmiller DR. Vasoactive intestinal peptide: cardiovascular effects. Cardiovasc Res 2001; 49: 27-37 [PMID: 11121793]

137 Polak JM, Bloom SR. Regulatory peptides of the gastrointestinal and respiratory tracts. Arch Int Pharmacodyn Ther 1986; 280: 16-49 [PMID: 2425759]

138 Duane J, Kom G, Wang. The neuropeptide vasoactive intestinal peptide: direct effects on immune cells and involvement in inflammatory and autoimmune diseases. Acta Physiol (Oxf) 2015; 213: 442-452 [PMID: 25422088 DOI: 10.1111/apha.12427]

139 Chedid P, Boussetta D, Pang DM, Belambrí SA, Marzaioli V, Fasseau M, Walker F, Cousineau A, El-Benna J, Marie JC. Vasoactive intestinal peptide dampens formyl-peptide-induced ROS production and inflammation by targeting a MAPK-p47<sup>phox</sup>/sup> phosphorylation pathway in monocytes. Mucosal Immunol 2017; 10: 332-340 [PMID: 27271317 DOI: 10.1038/mi.2016.51]

140 Delgado M, Ganea D. Cutting edge: is vasoactive intestinal peptide a type 2 cytokine? J Immunol 2001; 166: 2907-2912 [PMID: 11207237]

141 Leceta J, Martinez MC, Delgado M, Garrido E, Gomariz RP. Vasoactive intestinal peptide in immunomodulation. Pharmacol Rev 2004; 56: 249-290 [PMID: 15169929 DOI: 10.1124/pr.56.2.7]

142 Chorny A, Delgado M. Neuropeptides rescue mice from lethal sepsis by down-regulating secretion of the late-acting inflammatory mediator high mobility group box 1. Am J Pathol 2008; 172: 1297-1307 [PMID: 18385521 DOI: 10.2353/ajpath.2008.070969]

143 Delgado M, Ganea D. Neuropeptidergic effect of vasoactive intestinal peptide (VIP) in a mouse model of Parkinson’s disease by blocking microglial activation. FASEB J 2003; 17: 944-946 [PMID: 12626249 DOI: 10.1096/fj.02-7996f]

144 Delgado M, Ganea D. Vasoactive intestinal peptide inhibits IL-8 production in human monocytes. Biochim Biophys Acta 2003; 1601: 825-832 [PMID: 12589787]

145 Higino PM, Mendes PF, Miranda MB, Pereira DE, Mota AP, Nogueira Kde O, Caldas IS, Moura SA, Menezes CA. Vasoactive intestinal peptide reduces the inflammatory profile in mice infected with Trypanosoma cruzi. Exp Parasitol 2015; 159: 72-78 [PMID: 25358268 DOI: 10.1016/j.exppara.2015.08.084]

146 Ran WZ, Dong L, Tang CY, Zhou Y, Sun GY, Liu T, Liu YP, Guan CX. Vasoactive intestinal peptide suppresses macrophage-mediated inflammation by downregulating interleukin-17A expression via PKA- and PKC-dependent pathways. Int J Exp Pathol 2015; 96: 269-275 [PMID: 25944684 DOI: 10.1111/iep.12130]

147 Delgado M. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit the MEK1/MEK4/JNK signaling pathway in endotoxin-activated microglia. Biochem Biophys Res Commun 2002; 293: 771-776 [PMID: 12054537 DOI: 10.1006/sj.biophys.2001.0208]

148 Delgado M, Ganea D. Inhibition of endotoxin-induced macrophage chemokine production by VIP and PACAP in vitro and in vivo. Arch Physiol Biochem 2001; 109: 377-382 [PMID: 11935377 DOI: 10.1076/apab.109.4.377.4237]

149 Carrion M, Perea-Garcia S, Martínez C, Juarranz Y, Estrada-Capetillo L, Puig-Króger A, Gomariz RP, Gutiérrez-Cañas I. VIP impairs acquisition of the macrophage proinflammatory polarization profile. J Leukoc Biol 2016; 100: 1385-1393 [PMID: 27381006 DOI: 10.1189/jlb.3A0116-032KR]

150 Tametoko K, Mutt V. Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. Nature 1980; 285: 417-418 [PMID: 6892930]

151 Tametoko K. Isolation and characterization of peptide YY (PYY), a candidate gut hormone that inhibits pancreatic exocrine secretion.
El-Salhy M. Neuropeptide Y family of hormones: clinical relevance and potential use in gastrointestinal disease. Curr Top Med Chem 2007; 7:1710-1720 [PMID: 17979780]

El-Salhy M, Grimmelius L, Wilander E, Ryberg B, Terenius L, Lundberg JM, Tatemoto K. Immunocytochemical identification of polypeptide YY (PYY) cells in the human gastrointestinal tract. Histochemistry 1983; 77:15-23 [PMID: 6341321]

El-Salhy M, Wilander E, Grimmelius L, Terenius L, Lundberg JM, Tatemoto K. The distribution of polypeptide YY (PYY) - and pancreatic polypeptide (PP) - immunoreactive cells in the domestic fowl. Histochemistry 1982; 75:25-30 [PMID: 6896687]

El-Salhy M, Wilander E, Juntti-Berggren L, Grimmelius L. The distribution and ontology of polypeptide YY (PYY) - and pancreatic polypeptide (PP)-immunoreactive cells in the gastrointestinal tract of rat. Histochemistry 1983; 78:53-60 [PMID: 6547987]

El-Salhy M, Gundersen D, Gilja OH, Hatlebakk JG, Hausken T. Is irritable bowel syndrome an organic disorder? World J Gastroenterol 2014; 20: 384-400 [PMID: 24574708 DOI: 10.3734/wjg.v20.2.384]

Cox HM. Neuropeptide Y, Y1, Y2 and Y4 receptors mediate Y agonist responses in isolated human colon mucosa. Br J Pharmacol 2002; 135: 1505-1512 [PMID: 11906964 DOI: 10.1038/sj.bjp.0704604]

Cox HM. Polloel EL, Tough IR, Herzog H. Multiple Y receptors mediate pancreatic polypeptide responses in mouse colon mucosa. Peptides 2001; 22: 445-452 [PMID: 11287100]

Hyland NP, Cox HM. The regulation of veratrine-stimulated electric organ transport in mouse colon by neuropeptide Y (NPY), Y1 and Y2 receptors. Br J Pharmacol 2005; 146: 712-722 [PMID: 16100526 DOI: 10.1038/sj.bjp.0706368]

Hyland NP, Sjöberg F, Tough IR, Herzog H, Cox HM. Functional consequences of neuropeptide Y Y2 receptor knockout and Y2 antigen in mouse and human colonic tissues. Br J Pharmacol 2003; 139: 863-871 [PMID: 12813010 DOI: 10.1038/sj.bjp.0705298]

Wheway J, Mackay CR, Newton RA, Sainsbury A, Boey D, Herzog H, Mackay F. A fundamental bimodal role for neuropeptide Y1 receptor in the immune system. J Exp Med 2005; 202: 1527-1538 [PMID: 16330815 DOI: 10.1084/jem.20051971]

Chandrasekharan B, Nezami BG, Srinivasan S. Emerging neuropeptide targets in inflammation: NPY and VIP. Am J Physiol Gastrointest Liver Physiol 2013; 304: G499-G597 [PMID: 23538492 DOI: 10.1152/ajpgi.00493.2012]

Dimitrijevic M, Stanoevich S, Vujic V, Beck-Sickingler A, von Hörsten S. Neuropeptide Y and its receptor subtypes specifically modulate rat peritoneal macrophage functions in vitro: counter regulation through Y1 and Y2/5 receptors. Regul Pept 2005; 124: 163-172 [PMID: 15544855 DOI: 10.1016/j.regpep.2004.07.012]

Dimitrijevic M, Stanoevich S, Mitic K, Kustromovic N, Vujic V, Miletic T, Kovacevic-Jovanovic V. Modulation of granulocyte functions by peptide YY in the rat: age-related differences in Y receptors expression and plasma dipeptidyl peptidase 4 activity. Regul Pept 2010; 159: 100-109 [PMID: 19896984 DOI: 10.1016/j.regpep.2009.11.002]

Severini C, Imparta G, Falconieri-Erspar M, Salvadori S, Erspar M. The tachykinin peptide family. Pharmacol Rev 2002; 54: 285-322 [PMID: 12037144]

Ekblad E, Winther C, Ekman R, Håkanson R, Sundler F. Projections of peptide-containing neurons in rat small intestine. Neuroscience 1987; 20: 169-188 [PMID: 24368066]

Brodin E, Sjölund K, Håkanson R, Sundler F. Substance P-containing nerve fibers are numerous in human but not in feline intestinal mucosa. Gastroenterology 1983; 85: 557-564 [PMID: 6192036]

Lai JP, Douglas SD, Ho WZ. Human lymphocytes express substance P and its receptor. J Neuroimmunol 1998; 86: 80-86 [PMID: 9655475]

Lai JP, Douglas SD, Zhao M, Ho WZ. Quantification of substance P mRNA in human mononuclear phagocytes and lymphocytes using a mimic-based RT-PCR. J Immunol Methods 1999; 230: 149-157 [PMID: 10594362]

Marriott I, Bost KL. IL-4 and IFN-gamma up-regulate substance P receptor expression in murine peritoneal macrophages. J Immunol 2000; 165: 182-191 [PMID: 10861051]

Lambrecht BN, Gernprompr EA, Veraert EG, Carro-Muino I, De Veerman M, de Felipe C, Hunt SP, Thielemans K, Joos GF, Pauwels RA. Endogenously produced substance P contributes to lymphocyte proliferation induced by dendritic cells and direct TCR ligation. Eur J Immunol 1999; 29: 3815-3825 [DOI: 10.1002/eji.2000415213]

Metwali A, Blum AM, Ferraris L, Klein JS, Fiocchi C, Weinstock JV. Eosinophils within the healthy or inflamed human intestine produce substance P and vasoactive intestinal peptide. J Neuroimmunol 1994; 52: 69-78 [PMID: 7515901]

Weinstock JV, Blum A, Waldier J, Waldier R. Eosinophils from granulomas in murine schistosomiasis mansoni produce substance P. J Immunol 1988; 141: 961-966 [PMID: 2456338]

Masnaghi M, Marmalidou A, Tehrani M, Grace PM, Pothoulakis C, Dana R. Neuropeptide substance P and the immune response. Cell Mol Life Sci 2016; 73: 4249-4264 [PMID: 27314883 DOI: 10.1007/s00018-016-2293-z]

Guo CJ, Lai JP, Luo HM, Douglas SD, Ho WZ. Substance P up regulates macrophage inflammatory protein-1beta expression in human T lymphocytes. J Neuroimmunol 2002; 131: 160-167 [PMID: 12458047]

Sun J, Rannath RD, Zhi L, Tamizh selvi R, Bhatia M. Substance P enhances NF-kappaB transactivation and chemokine response in murine macrophages via ERK1/2 and p38 MAPK signaling pathways. Am J Physiol Cell Physiol 2008; 294: C1586-C1596 [PMID: 18434625 DOI: 10.1152/ajpcell.00129.2008]

Lembeck F, Holzer P. Substance P as a neurogenic mediator of antidiromic vasodilation and neurogenic plasma extravasation. Naunyn Schmiedebergs Arch Pharmacol 1979; 310: 175-183 [PMID: 93706]

Ahluwalia A, De Felipe C, O'Brien J, Hunt SP, Perretti M. Impaired IL-1beta-induced neutrophil accumulation in tachykinin NK1 receptor knockout mice. Br J Pharmacol 1998; 124: 1013-1015 [PMID: 9720767 DOI: 10.1038/sj.bjp.0701978]

Castellani ML, Vecchiet J, Salini V, Conti P, Theoharides TC, Caraffa A, Antonilfo P, Teté S, Ciampoli C, Cucurullo C, Cerulli G, Felaco M, Boscolo P. Stimulation of CCL2 (MCP-1) and CCL3 mRNA by substance P in LAD2 human mast cells. Transl Res 2009; 154: 27-33 [PMID: 19524871 DOI: 10.1016/j.trsl.2009.03.006]

O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F. The role of substance P in inflammatory disease. J Cell Physiol 2004; 201: 167-180 [PMID: 15334652 DOI: 10.1002/jcp.20061]

Gross KJ, Pothoulakis C. Role of neuropeptides in inflammatory bowel disease. Inflamm Bowel Dis 2007; 13: 918-932 [PMID: 17343284 DOI: 10.1002/ibd.20129]

Simeonidis S, Castagliuolo I, Pan A, Liu J, Wang CC, Mykoniatis A, Pasha A, Valenick LS, Sougioulitzis S, Zhao D, Pothoulakis C. Regulation of the NK-1 receptor gene expression in human macrophage cells via an NF-kappa B site on its promoter. Proc Natl Acad Sci USA 2003; 100: 2957-2962 [PMID: 12594338 DOI: 10.1073/pnas.2026384100]
192 Patel YC, Wheatley T, Ning C. Multiple forms of immunoreactive somatostatin: comparison of distribution in neural and nonneural tissues and portal plasma of the rat. Endocrinology 1981; 109: 1943–1949 [PMID: 6168257 DOI: 10.1210/po-109-6-1943]

193 Shulkes A. Somatostatin: physiology and clinical applications. Baillieres Clin Endocrinol Metab 1994; 8: 215–236 [PMID: 9709862]

194 Pennman E, Wass JA, Butler MG, Penny ES, Price J, Wu P, Rees LH. Distribution and characterisation of immunoreactive somatostatin in human gastrointestinal tract. Regal Pept 1983; 7: 53–65 [PMID: 6139847]

195 Ferone D, Resmini E, Boschetti M, Arvigo M, Albanez V, Ceresola E, Pivonello R, Albertelli M, Bianchi F, Giusti M, Minuto F. Potential indications for somatostatin analogues: immune system and lymphoproliferative disorders. J Endocrinol Invest 2005; 28: 111–117 [PMID: 16625859]

196 ten Bokum AM, Hofland LJ, van Hagen PM. Somatostatin and somatostatin receptor in the immune system: a review. Eur Cytokine Netw 2000; 11: 161–176 [PMID: 10905795]

197 Ferone D, Pivonello R, Kwokkeboom DJ, Gatto F, Ameri P, Colao A, de Krijger RR, Minuto F, Lamberts SW, van Hagen PM, Hofland LJ. Immunohistochemical localization and quantitative expression of somatostatin receptors in normal human spleen and thymus: Implications for the in vivo visualization during somatostatin receptor scintigraphy. J Endocrinol Invest 2012; 35: 528–534 [PMID: 21765239 DOI: 10.3275/7871]

198 Dalm VA, van Hagen PM, van Koetsveld PM, Achilleu S, Houtsmailler AB, Pols DH, van der Lely AJ, Lamberts SW, Hofland LJ. Expression of somatostatin, cortistatin, and somatostatin receptor subtypes in human macrophages, macrophages, and dendritic cells. Am J Physiol Endocrinol Metab 2003; 285: E444–E453 [PMID: 12684217 DOI: 10.1152/ajpendo.00406.2001]

199 Dalm VA, van Hagen PM, van Koetsveld PM, Achilleu S, Houtsmailler AB, Pols DH, van der Lely AJ, Lamberts SW, Hofland LJ. Differential expression of somatostatin receptor subtypes in human peripheral blood mononuclear cell subsets. Eur J Endocrinol 2004; 150: 565–577 [PMID: 15080788]

Hagströmer L, Entestam L, Stridsberg M, Talm E. Expression pattern of somatostatin receptor subtypes 1-5 in human skin: an immunohistochemical study of healthy subjects and patients with psoriasis or atopic dermatitis. Exp Dermatol 2006; 15: 950–957 [PMID: 17083361 DOI: 10.1111/j.1600-0625.2006.00487.x]

200 Talme T, Ivanoff J, Håggglund M, Van Neerven RJ, Ivanoff A, Avignon K. Somatostatin receptor (SSTR) expression and function in normal and leukemic T-cells. Evidence for selective effects on adhesion to extracellular matrix components via SSTR2 and/or 3. Cytokine Netw 2001; 12S: 71–79 [PMID: 11472428]

201 Rosskopf D, Schürks M, Manthey I, Joisten M, Busch S, Siffert W. Signal transduction of somatostatin in human B lymphoblasts. Am J Physiol Cell Physiol 2003; 284: C179–C190 [PMID: 12388115 DOI: 10.1152/ajpcell.01606.2001]

202 Casnici C, Lattuada D, Pevergo C, Franco P, Marelli O. Inhibitory effect of somatostatin on human T lymphocytes proliferation. Int J Immunopharmacol 1997; 19: 721–727 [PMID: 9669213]

203 Radosović-Stasić B, Trobonjaca Z, Lucin P, Ćuk M, Polić B, Rukavin D. Immunosuppressive and antiproliferative effects of somatostatin analog SMS 201-995. Int J Neurosci 1995; 81: 283–297 [PMID: 7628916]

204 Siriani MC, Annibale B, Fain S, Delle Fave G. Inhibitory effect of somatostatin on pancreatic and/or 3. Cytokine Netw 2001; 12S: 71–79 [PMID: 11472428]

205 Eglezos A, Andrews PV, Helme RD. In vivo inhibition of the rat primary antibody response to antigenic stimulation by somatostatin. Immunol Cell Biol 1993; 71: 125–129 [PMID: 7683630 DOI: 10.1038/icb.1993.13]

206 Goetz EJ, Payan DG. Inhibition by somatostatin of the release of mediators from human basophils and rat leukemic basophils. J Immunol 1984; 133: 3255–3259 [PMID: 6208274]

207 Payan DG, Hess CA, Goetzl EJ. Inhibition of somatostatin of the proliferation of T-lymphocytes and MOLT-4 lymphoblasts. Cell Immunol 1984; 84: 433–438 [PMID: 6142770]
Korbonits M, Goldstone AP, Gueorguiev M, Grossman AB. Ghrelin–a hormone with multiple functions. Front Neuroendocrinol 2004; 25: 27–68 [PMID: 15183037 DOI: 10.1016/j.yfrne.2004.05.002]

Wasseem T, Duckworth M, Ito H, Ashley SW, Robinson MK. Exogenous ghrelin modulates release of pro-inflammatory and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. Surgery 2008; 143: 334–342 [PMID: 18291254 DOI: 10.1016/j.surg.2007.09.039]

Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakhthivel SK, Palaniappan R, Lillard JW Jr, Taub DD. Ghrelin inhibits leptin- and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. Surgery 2008; 143: 334–342 [PMID: 18291254 DOI: 10.1016/j.surg.2007.09.039]

Peracchi M, Bardella MT, Caprioli F, Massironi S, Conte F, Drew K, McAlindon ME, Lobo AJ, Sanders DS. Maldonado E, Valle-Rios R, Feintuch-Unger JH, Schnoor M, Meraz-Ríos MA, Citalán-Madrid AF, Hernández-Ruíz M, Reyes-Martínez AA, Fernandez-Martinez IE, Candelario-Martínez AA, Villegas-Sepúlveda N, Medina-Contreras O, Nava P. The pro-inflammatory cytokines IFNγ/TNFα increase chromogranin A, chromogranin B, and secretoneurin in collagenous colitis. Inflamm Bowel Dis 2013; 19: 855–861 [PMID: 23423580 DOI: 10.1007/s10575-013-0612-4]

El-Salhy M, Vassari S. Gastric inhibits leptin- and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. Surgery 2008; 143: 334–342 [PMID: 18291254 DOI: 10.1016/j.surg.2007.09.039]

Palaniappan R, Lillard JW Jr, Taub DD. Ghrelin inhibits leptin- and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. Surgery 2008; 143: 334–342 [PMID: 18291254 DOI: 10.1016/j.surg.2007.09.039]
El-Salhy M et al. GI neuroendocrine peptides/amines and IBD

M, Jones D, Gewirtz AT, Sitaraman SV, Srinivasan S. Targeted deletion of neurotrophin Y (NPY) modulates experimental colitis. PLoS One 2008; 3: e3304 [PMID: 18636554 DOI: 10.1371/journal.pone.0003304]

257 Björck S, Jennische E, Dahlström A, Ahlman H. Influence of topical rectal application of drugs on dextran sulphate-induced colitis in rats. Dig Dis Sci 1997; 42: 824-832 [PMID: 9125657]

258 El-Salhy M, Mazzawi T, Umezawa K, Gilja OH. Enteroendocrine cells, stem cells and differentiation progenitors in rats with TNBS-induced colitis. Int J Mol Med 2016; 38: 1743-1751 [PMID: 27779708 DOI: 10.3892/ijmm.2016.2787]

259 Koch TR, Carney JA, Go VL. Distribution and quantitation of gut neuropeptides in normal intestine and inflammatory bowel diseases. Dig Dis Sci 1987; 32: 369-376 [PMID: 2435473]

260 Bernstein CN, Robert ME, Eysselein VE. Rectal substance P concentrations are increased in ulcerative colitis but not in Crohn's disease. Am J Gastroenterol 1993; 88: 908-913 [PMID: 7684884]

261 Sjölund K, Schaffalitzky OB, Muckeberg DE, Fahrenkrug J, Håkanson R, Petersen BG, Sundler F. Peptide-containing nerve fibres in the gut wall in Crohn's disease. Gut 1983; 24: 724-733 [PMID: 6190243]

262 Kimura K, Chen D, Lindström E, Yamada H, Zhao CM, Håkanson R. Functional impairment of the individual rat stomach ECL cell in response to sustained hypergastrinemia. Regul Pept 1997; 72: 69-77 [PMID: 9652979]

263 Watanabe T, Kubota Y, Sawada T, Muto T. Distribution and quantification of somatostatin in inflammatory disease. Dis Colon Rectum 1992; 35: 488-494 [PMID: 1348980]

264 Koch TR, Carney JA, Morris VA, Go VL. Somatostatin in the idiopathic inflammatory bowel diseases. Dis Colon Rectum 1988; 31: 198-203 [PMID: 2894053]

265 Ahoon A, Kysöla A, Penttilä O. Enterochromaffin cells in macrophages in ulcerative colitis and irritable colon. Ann Clin Res 1976; 8: 1-7 [PMID: 937988]

266 Eissa N, Ghia JE. Immunomodulatory effect of ghrelin in the intestinal mucosa. Neurogastroenterol Motil 2015; 27: 1519-1527 [PMID: 26503163 DOI: 10.1111/nmo.12703]

267 Karmiris K, Koutroubakis IE, Xidakis C, Polychronaki M, Voudouri T, Kouroumalas EA. Circulating levels of leptin, adiponectin, resistin, and ghrelin in inflammatory bowel disease. Inflamm Bowel Dis 2006; 12: 100-105 [PMID: 16432373 DOI: 10.1097/01.mib.0000200345.38837.46]

268 Ates Y, Degertiok B, Erdil A, Yaman H, Dagkalp G. Serum ghrelin levels in inflammatory bowel disease with relation to disease activity and nutritional status. Dig Dis Sci 2008; 53: 2215-2221 [PMID: 18259977 DOI: 10.1007/s10620-007-0113-x]

269 Hosomi S, Oshitani N, Kamata N, Sogawa M, Yamagami H, Watanabe T, Konimasa K, Fujimori R, Guedes NN, Chiba T. Candidate markers for stem and early progenitor cells, Musashi-1 and Nestin, are expressed in crypt base columnar cells of small mouse intestine. FEBS Lett 2005; 535: 131-135 [PMID: 12560091]

270 He XC, Yin T, Grindley JC, Tian Q, Sato T, Tao WA, Dirisina R, Porter-Westphal KS, Hembree B, Johnson T, Wiedemann LM, Barrett TA, Hool L, Wu H, Li L. PTPN- deficient intestinal stem cells initiate intestinal polyposis. Nat Genet 2007; 39: 189-198 [PMID: 17279774 DOI: 10.1038/ng1928]

271 Yang Q, Berningham NA, Finegold MJ, Zoghbi HY. Requirement of Math1 for secretory cell lineage commitment in the intestine. Science 2001; 294: 2155-2158 [PMID: 11739954 DOI: 10.1126/science.1065718]

272 Jenny M, Uhl C, Roche C, Dulac I, Guillemin V, Guillermot F, Jensen J, Keding M, Gradwohl G. Neurogenin is differentially required for endocrine cell fate specification in the intestinal and gastric epithelium. EMBO J 2002; 21: 6338-6347 [PMID: 12456641]

273 Wang J, Cortina G, Wu SV, Tran R, Cho JH, Tsai MJ, Bailey TJ, Jamrich M, Ament ME, Treem WR, Hill ID, Varghese G, Gershman G, Farmer DG, Reyen L, Martin MG. Mutant neurogenin-3 in congenital malabsorptive diarrhea. N Engl J Med 2006; 355: 270-280 [PMID: 16855267 DOI: 10.1056/NEJMoa054288]

274 Lee CS, Perreault N, Brestelli JE, Kaestner KH. Neurogenin 3 is essential for the proper specification of gastric endoendocrine cells and the maintenance of gastric endoendocrine cell identity. Genesis 2002; 16: 1488-1497 [PMID: 12908087 DOI: 10.1016/s1056-6854(01)00106-7]

275 Naya FJ, Huang HP, Qiu Y, Mutoh H, DeMayo FJ, Leiter AB, Tsai MJ. Diabetes, defective pancreatic morphogenesis, and abnormal endoendocrine differentiation in BET2a/NeuroD-deficient mice. Genetics 1997; 11: 2323-2334 [PMID: 930861]

276 Ahlgren U, Jonsson J, Edlund H. The morphogenesis of the pancreatic mesenchyme is uncoupled from that of the pancreatic
epithelium in IPF1/PDX1-deficient mice. Development 1996; 122: 1409-1416 [PMID: 8625829]

293 Schonhoff SE, Giel-Moloney M, Leiter AB. Neurogenin 3-expressing progenitor cells in the gastrointestinal tract differentiate into both endocrine and non-endocrine cell types. Dev Biol 2004; 270: 443-454 [PMID: 15183725 DOI: 10.1016/j.ydbio.2004.03.013]

294 Fakhfouri G, Rahimian R, Daneshmand A, Bahremand A, Rasouli MR, Dehpour AR, Mehr SE, Mousavizadeh K. Granisetron ameliorates acetic acid-induced colitis in rats. Hum Exp Toxicol 2010; 29: 321-328 [PMID: 20154102 DOI: 10.1177/0960327110362702]

295 Mousavizadeh K, Rahimian R, Fakhfouri G, Aslani FS, Ghafourifar P. Anti-inflammatory effects of 5-HT receptor antagonist, tropisetron on experimental colitis in rats. Eur J Clin Invest 2009; 39: 375-383 [PMID: 19302562 DOI: 10.1111/j.1365-2362.2009.02102.x]

296 Vega Lde L, Muñoz E, Calzado MA, Lieb K, Candelario-Jalil E, Gschaidmeir H, Färber L, Mueller W, Stratz T, Fiebich BL. The 5-HT3 receptor antagonist tropisetron inhibits T cell activation by targeting the calcineurin pathway. Biochem Pharmacol 2005; 70: 369-380 [PMID: 15922994 DOI: 10.1016/j.bcp.2005.04.031]

297 Motavallian-Naeini A, Minaiyan M, Rabbani M, Mahzuni P. Anti-inflammatory effect of ondansetron through 5-HT3 receptors on TNBS-induced colitis in rats. EXCLI J 2012; 11: 30-44 [PMID: 27350767]

298 Kato S. Role of serotonin 5-HT: receptors in intestinal inflammation. Biol Pharm Bull 2013; 36: 1406-1409 [PMID: 23995650]

299 Fakhfouri G, Rahimian R, Ghia JE, Khan WI, Dehpour AR. Impact of 5-HT3 receptor antagonists on peripheral and central diseases. Drug Discov Today 2012; 17: 741-747 [PMID: 22390046 DOI: 10.1016/j.drudis.2012.02.009]

300 Kim JJ, Bridle BW, Ghia JE, Wang H, Syed SN, Manocha MM, Rengasamy P, Shajib MS, Wan Y, Hedlund PB, Khan WI. Targeted inhibition of serotonin type 7 (5-HT7) receptor function modulates immune responses and reduces the severity of intestinal inflammation. J Immunol 2013; 190: 4795-4804 [PMID: 23554310 DOI: 10.4049/jimmunol.1201887]

301 Levin AD, van den Brink GR. Selective inhibition of mucosal serotonin as treatment for IBD? Gut 2014; 63: 866-867 [PMID: 23868328 DOI: 10.1136/gutjnl-2013-305283]

302 Chu TG, Orlowski M. Soluble metalloendopeptidase from rat brain: action on enkephalin-containing peptides and other bioactive peptides. Endocrinology 1985; 116: 1418-1425 [PMID: 3882408 DOI: 10.1210/endo-116-4-1418]

303 Bloom SR, Polak JM, Pearse AG. Vasoactive intestinal peptide and watery-diarrhoea syndrome. Lancet 1973; 2: 14-16 [PMID: 4123289]

304 Balasubramaniam AA. Neuropeptide Y family of hormones: receptor subtypes and antagonists. Peptides 1997; 18: 445-457 [PMID: 9145434]

305 Agro A, Stanisz AM. Inhibition of murine intestinal inflammation by anti-substance P antibody. Reg Immunol 1993; 5: 120-126 [PMID: 7692913]

306 Kataeva G, Agro A, Stanisz AM. Substance-P-mediated intestinal inflammation: inhibitory effects of CP 96,345 and SMS 201-995. Neuroimmunomodulation 1994; 1: 350-356 [PMID: 7545531]

307 Gonzalez-Rey E, Cherny A, Delgado M. Therapeutic action of ghrelin in a mouse model of colitis. Gastroenterology 2006; 130: 1707-1720 [PMID: 16697735 DOI: 10.1053/j.gastro.2006.01.041]
