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Enteric Nervous System in the Small Intestine: Pathophysiology and Clinical Implications

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Abstract

The digestive system is endowed with its own, local nervous system, referred to as the enteric nervous system (ENS). Given the varied functions of small intestine, its ENS has developed individualized characteristics relating to motility, secretion, digestion, and inflammation. The ENS regulates the major enteric processes such as immune response, detecting nutrients, motility, microvascular circulation, intestinal barrier function, and epithelial secretion of fluids, ions, and bioactive peptides. Remarkable progress has been made in understanding the signaling pathways in this complex system and how they work. In this article, we focus on recent advances that have led to new insights into small intestinal ENS function and the development of new therapies.

Keywords

Enteric nervous system; Small intestine; Neurotransmitters; Intestinal secretion; Irritable bowel syndromes; Inflammatory bowel disease; Diabetes mellitus

Introduction

The enteric nervous system (ENS) is the largest and most complex subdivision of the peripheral nervous system [1]. The principal components of the ENS are the myenteric (Auerbach) and the submucosal (Meissner) plexuses. The myenteric plexus, located between the longitudinal and circular smooth muscle layers, mainly regulates the relaxation and contraction of the intestinal wall. The submucosal (Meissner) plexus senses the lumen environment and regulates gastrointestinal blood flow as well as controlling the epithelial cell functions and secretion. Three classes of enteric neurons can be identified in the ENS, including motor neurons, intrinsic primary afferent neurons (IPANs, or sensory neurons), and interneurons. IPANs are the primary sensors and regulators of the ENS that detect the chemical features of the luminal contents and physical state of the organs (ie, tension in the enteric wall). These cells connect with each other, with interneurons, and with motor neurons (either excitatory or inhibitory).

In addition to neurons, the ENS contains an extensive component population of enteric glia with functional similarities to astroglia of the brain. Enteric glial cells (EGC) represent the most abundant non-neuronal cell type within ENS that have a significant role in forming a diffusion barrier around the capillaries surrounding ganglia similar to that of blood-brain barrier. Interstitial cells of Cajal (ICC) are also related to ENS and are electrically coupled to

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the muscle. These pacemaker cells generate spontaneous electrical slow waves and mediate inputs from motor neurons.

The small intestinal ENS has developed specific properties and functions because of the distinct role and anatomy of small intestine. The fasting small bowel contractions are organized into a pattern called the migrating motor complex (MMC), which consists of three distinctive motility patterns of neuromuscular quiescence (phase 1), irregular contractions varying in amplitude and periodicity (phase 2), and the distinct pattern of uninterrupted propagating contractions (phase 3). The onset and migration of the MMC in the small bowel are under control of the ENS and are independent of extrinsic control. Therefore, disorders affecting the viability and function of enteric neurons readily cause intestinal motility disorders. In this article, we describe the role of the small intestinal ENS in normal and pathologic states with focus on peristalsis, inflammation, secretion, and pain perception, and we review the emerging approaches for treating their related disorders.

Development and Aging of the ENS in the Small Intestine

In vertebrates, enteric precursors of the ENS originate from the neural crest and migrate into the digestive system. In mice, ENS neurons form during the early postnatal period and continue through day P21 [2•]. The ENS, however, continues to enlarge thereafter as the bowel grows in length and diameter, suggesting that neurons continue to be generated. An ever increasing range of molecules are being found in the process of ENS development [3]. Several growth factors influence the proliferation, differentiation, and survival of the ENS, including glial cell line-derived neurotrophic factor (GDNF), neurturin, neurotrophin-3, and Sonic hedgehog [4]. GDNF and its receptor components (GFR- α and RET) play a crucial role in the survival of enteric neurons [5]. Other peptides such as cannabinoids and some serotonin (5-HT) subtypes are also involved in neuronal development and proliferation [2•]. Knowing the developmental characteristics of ENS provides insight to the process of aging. However, some pathologic conditions such as parkinsonism, diabetes, and vascular diseases might simultaneously affect the normal aging process in ENS, and therefore these conditions should be considered separately.

The clinical manifestation of aging in ENS includes constipation, incontinence, and evacuation disorders. It is now evident that unlike other regions of the peripheral nervous system, the ENS exhibits a neuronal loss during aging, predominantly of cholinergic neurones and ICCs, whereas nitrergic myenteric neurons remain selectively protected (although with partial loss of function and axonal swelling) [6•, 7]. Furthermore, it has been shown that in the jejunum of middle-aged rats, the participation of vasoactive intestinal peptide (VIP) in functional nonadrenergic noncholinergic (NANC) innervation is increased, while functional innervation with substance P (SP) is decreased [8]. The mechanisms of aging are not yet completely understood; however, long-term exposure to free radicals, decrease in neurotrophic factors, and loss of appropriate cell-to-cell interactions are known to be causal factors in the aging process [9].

The ENS and Peristalsis in the Small Intestine

The local control of the ENS over mixing and propulsive movements in the small intestine is exerted through an intense interaction between its different neuronal cell types. As previously mentioned, the small bowel has its particular contraction pattern (the MMC), which is under control of the ENS.

Cells and neurotransmitters

Most of the neurotransmitters secreted by the ENS are identical to those found in the central nervous system (eg. acetylcholine, dopamine, and serotonin). Like the central nervous system, the ENS neurons secrete acetylcholine and neuropeptides, but not noradrenaline. In general, neurons that secrete acetylcholine and SP are excitatory, which stimulate smooth muscle contraction, increase intestinal secretions, release enteric hormones, and dilate blood vessels. Norepinephrine is derived from extrinsic sympathetic neurons and its effect is almost always inhibitory. NANC neurotransmission also plays a significant role in the peristaltic reflex of the gastrointestinal tract and is critical to intestinal motility. NANC is an important neurotransmitter system acting via VIP, nitric oxide (NO), and SP. An intense interaction occurs between these enteric neurotransmitters, in that each can influence the production, release, and effects of the other. VIP and NO appear to be the dominant inhibitory NANC neurotransmitters in the ENS, whereas SP is an excitatory neurotransmitter. Bile acids (BAs) have well-known actions on intestinal motility and secretion [10], and are hypothesized to activate intestinal BA receptor, G protein-coupled bile acid receptor 1 (GpBAR₁) on inhibitory motor neurons to release NO and suppress motility [11••].

Galanin is a neuropeptide that exerts a variety of cellular functions in the nervous system. In the ENS, galanin is hypothesized to influence the gastrointestinal motility by inhibition of acetylcholine and SP release from excitatory motor neurons and secretion through galanin 1 receptors (GAL-R₁) [12]. Pham et al. [12] showed that GAL-R₁ is localized to an abundant population of VIP submucous neurons of the small intestine. Elevation of galanin is also suggested as a marker of nerve damage in humans. GAL-R₁ expression by enteric epithelia is up-regulated by the transcription factor nuclear factor- κ B (NF- κ B). In a study on colonic inflammation, SP, neuropeptide K (N-terminally extended form of neurokinin A), and galanin showed significant increase, which mostly subsided in the long term with only galanin remaining significantly elevated in the mucosa [13]. The mechanism of long-term increase in galanin is currently unknown.

Postoperative ileus and related dysfunctions

Surgical manipulation of the intestine activates the macrophages to release NO and prostaglandins through inducible nitric oxide synthase (NOS) and cyclo-oxygenase-2 (COX-2), respectively. Intestinal manipulations also induce the secretion of proinflammatory cytokines which, in turn, affect enteric motility [14]. On the other hand, it has been shown that interruption of gastrointestinal motility in a rat model of ileus is markedly reduced by using COX-2 inhibitors and thereby inhibiting the release of prostaglandins from inflammatory cells in the bowel wall [15]. In a recent randomized, double-blind, controlled trial, Wattchow et al. [16•] showed that perioperative low-dose celecoxib markedly reduced the development of paralytic ileus following major abdominal surgery. However, it did not accelerate early recovery of bowel function.

Adenosine is involved in the pathophysiology of intestinal disorders, particularly postoperative ileus and related dysfunctions. Adenosine A₁ receptor blockade is shown to reverse experimental postoperative ileus in rat colon [17]. Other studies have shown a significant involvement of adenosine in the control of intestinal secretion, motility, and sensation, via activation of A₁, A_{2A}, A_{2B} or A₃ purinergic receptors, and the participation of adenosine triphosphate (ATP) in the regulation of enteric functions, through the recruitment of P_{2X} and P_{2Y} receptors [18].

Diabetes

Diabetes can result in loss of enteric neurons as well as neuronal dysfunction and subsequent gastrointestinal complications [19]. This condition is associated with the development of autonomic neuropathy affecting the intrinsic neurons, ICCs, and smooth muscle [20]. Neuronal apoptosis appears to contribute to the neurodegeneration seen in animal and cell culture models of diabetes [21]. It is hypothesized that high glucose levels result in depolarization of neurons and increased intracellular calcium, which might explain in part the mechanism of glucotoxicity in enteric neurons [22]. Alterations in insulin signaling and tyrosine kinase activity as well as reduction in neurotrophic factor support have been implicated in the pathophysiology of diabetic complications. Immediate insulin treatment is shown to prevent gut motility alterations and loss of nitrergic neurons in the ileum and colon of rats with streptozotocin-induced diabetes [23•]. Anitha et al. [19] showed that GDNF reverses the morphological and functional effects of hyperglycemia on enteric neuronal survival. Neuropeptide Y (NPY) is another important peptide regulating gastrointestinal motility with profound effects on neuronal proliferation at early developmental stages and on survival at later stages. GDNF is shown to modulate enteric neuronal survival and proliferation through NPY expression, which may be a potential therapeutic target for gastrointestinal motility disorders in diabetes [24].

Diabetes also affects the function of neurons in terms of the intense interaction between enteric neurotransmitters. VIP as inhibitory NANC neurotransmitter in the ENS is present at low levels in the intestinal tissue of diabetic rats, which contributes in part to the abnormal motility observed [25].

Parkinson's disease

Gastrointestinal dysfunction is the most common nonmotor symptom of Parkinson's disease. Patients with Parkinson's disease experience symptoms that span the entire gastrointestinal tract, including abnormal salivation, dysphagia, delayed gastric emptying, constipation, and defecatory dysfunction [26]. Parkinson's disease traditionally was considered a disease of dopaminergic neurons in the substantia nigra; however, pathological analyses of gastrointestinal samples from these patients also suggest neuronal loss in the ENS [27]. Electrophysiological recording of neural-mediated muscle contraction in isolated colons from animals treated with MPTP (the prototypical parkinsonian neurotoxin) confirmed a relaxation defect associated with dopaminergic degeneration [28]. Greene et al. [29] demonstrated that parkinsonian neurotoxin and mitochondrial complex I inhibitor rotenone cause delayed gastric emptying and enteric neuronal dysfunction in the absence of major motor dysfunction or CNS pathology when administered chronically to rats.

The ENS and Pain Perception in the Small Intestine

Pain is an important manifestation of inflammation in ENS because inflammatory cytokines and mediators sensitize primary afferent neurons. Changing luminal contents continuously activate intrinsic and extrinsic afferent neurons that project to the enteric and central nervous system, respectively. In some disease states, the stimulus-response function sensitizes afferent pathways in the way that a low-intensity stimuli normally not perceived is felt as painful and noxious [30•].

Cells and neurotransmitters

Serotonin, prostaglandin, cannabinoids, bradykinin, ATP, and several other signaling molecules are released during intestinal inflammation or injury which can rapidly alter neuron properties [30•, 31]. Serotonin is a main neurotransmitter related to pain perception and initiation of peristalsis and secretory reflexes [32]. It has been shown to affect functions

of the digestive system through activation of several different receptor types, of which 5-HT₃, 5-HT₄, and 5-HT_{1b} are the most important for gastrointestinal function. Adenosine is another modulator of intestinal ENS function with dual control over pain transmission. Research in animal models shows that the stimulation of A1 or A2A receptors induced an inhibitory or facilitatory effect, respectively, on pain perception [33].

Although the neurotransmitters mentioned above are implicated in pain sensitization, their rapid and transient increase cannot explain the lasting changes observed in disease-related hypersensitivity. In fact, these prolonged effects are suggested to be mediated by neurotrophic factors. Most of these molecules (eg, GDNF family and nerve growth factor) produce sensitization of sensory neurons that can convert non-noxious stimuli into pain-producing stimuli. Consistent with its role in the development of hypersensitivity, nerve growth factor (NGF) levels increase during several inflammatory disorders, and neutralizing NGF antibodies block the enhanced responses to colorectal distension [34]. It was demonstrated that mediators released from colonic mucosal biopsy samples of patients with irritable bowel syndrome (IBS) excite neurons of the human submucosal plexus. The activation requires histamine, serotonin, and proteases, and is not associated with IBS subtype [35].

Irritable bowel syndrome

IBS is a disorder of the brain-gut link associated with exaggerated response to stress; characteristic symptoms include abdominal pain/discomfort and concurrent disturbance in defecation. Because IBS dominantly involves mothers and their children, researchers have attempted to find the genetic inheritance pattern of the disease. Mitochondrial DNA is a circular ring of DNA found in mitochondria, which is inherited only from the mother. Camilleri et al. [36•] studied the possibility that mitochondrial DNA single nucleotide polymorphisms could confer risk to the development of IBS, and suggested that variation in mitochondrial DNA may be associated with satiation, gastric emptying, and possibly pain. Recent clinical investigations of IBS have identified novel therapeutic approaches that modulate the serotonin-mediated control of the ENS. Generally, activation of 5-HT_{2B}, 5-HT₃, or 5-HT₄ receptors on enteric cholinergic neurons results in acetylcholine release and smooth muscle contraction. On the other hand, serotonin stimulates 5-HT₄, 5-HT_{1A}, or 5-HT_{1D} receptors on inhibitory enteric or nitrergic neurons to release NO and subsequently cause smooth muscle relaxation [37]. Table 1 summarizes new drugs used for IBS treatment [38•, 39–41, 42•, 43•]. Transient receptor potential vanilloid type I (TRPV1 or VR1) receptor has gained attention regarding its prominent role in inflammation-induced pain and visceral hypersensitivity. However, there are concerns with its antagonists PMG51749 and AMG517 hyperthermia because of their effects on thermoregulation [43•].

Hydrogen sulfide (H₂S) is an endogenous gasotransmitter (gaseous neurotransmitter), which exerts different effects in the digestive system, including relaxation of ileal smooth muscle and stimulation of intestinal secretion and nociceptive processes [44]. By far, H₂S is implicated as an agent both preventing and causing tissue damage and inflammation. The latter effect appears to be mediated via activation of K_{ATP} channels and to be NO dependent [45•].

The ENS and Secretion in the Small Intestine

The main physiological task of enteric secretion is the continuous hydration of luminal contents to ensure appropriate mixing and absorption of nutrients and effective protection against potentially harmful pathogens or enterotoxins. The intestinal crypt cells secrete chloride into the lumen, resulting in accumulation of fluid. The regulation of chloride secretion occurs by neural reflex pathways within the ENS.

Cells and neurotransmitters

Multiple cell surface receptors are involved in intestinal secretion [46]. The intestinal secretory reflexes arise from complex interactions between excitatory and inhibitory neurotransmitters, released by both the ENS and afferent neurons (Table 2). However, intestinal secretion is also modulated by a variety of messengers released from epithelial, endocrine, and immune cells.

Firing of secretomotor neurons releases acetylcholine or VIP, which stimulates secretion of Cl^- and HCO_3^- , as well as fluid secretion from epithelial cells. It is now apparent that mechanical stimulation releases 5-HT from enterochromaffin cells with subsequent activation of cholinergic and VIP secretomotor neurons. Pathophysiological changes in these signaling mechanisms contribute to disorders of motility and secretion. 5-HT is also involved in carcinoid diarrhea, cholera toxin, and bile salt-induced fluid and electrolyte secretion by activating the ENS.

Diarrhea

Diarrhea is characterized by frequent loose or liquid bowel movements. It can represent a symptom of diseases such as inflammatory bowel disease (IBD), intestinal ischemia, celiac disease, infection, or functional bowel disorders. Understanding secretomotor neurons is basic to understanding neurogenic secretory diarrhea, constipation, and therapeutic strategies. Hyperactivity of secretomotor neuronal activity elevates Cl^- secretion and induces neurogenic secretory diarrhea. Secretory diarrhea results from increased chloride secretion, decreased sodium absorption, or increased mucosal permeability. Cholera, the prototype of secretory diarrhea, is caused by the enterotoxin of *Vibrio cholerae* (cholera toxin). Cholera toxin strongly activates adenylyl cyclase, causing a prolonged increase in intracellular concentration of cyclic adenosine monophosphate (AMP) within crypt enterocytes. Continuous cAMP production activates chloride channels, resulting in unabated water and electrolyte secretion that leads to voluminous watery diarrhea. Additionally, cholera toxin affects the ENS, resulting in an independent stimulus of secretion. Gwynne et al. [47] recently showed that cholera toxin induces specific and sustained hyperexcitability of secretomotor neurons in enteric pathways. This effect of cholera toxin depends on 5-HT₃, nicotinic, and neurokinin 1 receptors. Cholera toxin is thought to activate neural pathways via release of 5-HT from enterochromaffin cells, which depends on 5-HT₃ receptors. Hyperactivity of secretomotor neuronal activity also elevates Cl^- secretion and induces neurogenic secretory diarrhea. In food allergies and inflammatory states, mast cell mediators, including histamine, serotonin, and prostaglandins, elevate secretomotor firing, which in turn stimulates the secretion of NaCl and large volumes of H₂O.

The ENS and Inflammation in the Small Intestine

Inflammation causes significant changes in intestinal functions including motility, secretion, and sensation [48]. The interplay between ENS and inflammation highlights the existence of close interactions between ENS and enteric immune cells. In this scenario, EGCs play an important role in enteric permeability, because extreme cases of inflammation and necrosis occur in the absence of glial cell function. Patients with chronic IBD display varying levels of enteric inflammation, and enteric ganglionitis is reported in some patients with severe IBS. Elevated intestinal permeability is apparent in patients with Crohn's disease, necrotizing enterocolitis, diabetes, and IBS. This is in accordance with the fact that IBS symptoms are more frequent in IBD patients than in the general population [49••].

Cells and neurotransmitters

Ample evidence exists that gastrointestinal inflammation is related to an imbalance in the function of peptidergic neurons, including SP, VIP, and NPY [50]. EGCs increase GDNF secretion during intestinal inflammation, which could act to protect intestinal epithelial cells from cytokine-induced apoptosis. Glucagon-like peptide-2 (GLP-2) is an important regulator of nutritional absorptive capacity with cell differentiation properties and anti-inflammatory actions, which is produced by various ENS neurons. In animal models of IBD, GLP-2 significantly improves mucosal inflammation indices, reduces levels of inflammatory cytokines (interferon- γ , tumor necrosis factor- α , interleukin [IL]-1 β) and inducible NOS, and increases levels of IL-10 [51]. GLP-2 probably reduces intestinal mucosal inflammation by activation of VIP neurons of the submucosal plexus.

IBD and neurogenic inflammation

Pathologic changes of the ENS in IBD include hypertrophy, hyperplasia, and axonal damage to nerve fibers and neuronal cell bodies, and hyperplasia of EGCs [52].

Enteric neurons can directly secrete inflammatory mediators (eg, IL-8). A similar role could be played by EGCs as they respond to intestinal inflammation by proliferating and producing inflammatory cytokines (eg, IL-6). Conversely, EGCs could inhibit inflammation as they secrete mediators (eg, nerve growth factor and neurotrophin-3) that have anti-inflammatory properties in animal models of colitis. EGCs seem to be active elements of the ENS during intestinal inflammatory and immune responses by acting as antigen-presenting cells and interacting with the mucosal immune system via the expression of cytokines and cytokine receptors. Specific ablation of EGCs leads to a breakdown of the epithelium barrier, suggesting a role of EGCs in maintaining the integrity or permeability of the mucosa [53]. Neurogenic inflammation refers to an inflammatory reflex arc by sensory neurons, which transmits noxious stimulus centrally and results in both pain perception and an intense local inflammatory reaction. Inflammation affects neuronal function and survival; conversely, neurogenic inflammation has been suggested to play a key role in the pathogenesis of IBD. Porcher et al. [54] described the almost complete abolition of ICCs within the longitudinal and circular muscle layers in Crohn's disease, and a significant reduction in numbers within the myenteric and deep muscular plexuses. These changes may explain the development of dysmotility in some patients. In an interesting study, Takami et al. [55•] showed that surgical denervation performed before chemical induction of IBD suppresses the score in all of the inflammatory indices such that almost no sign of inflammation is observed in histological evaluation.

NPY is widely expressed in the central and peripheral nervous system and is involved in the regulation of several physiological processes, including energy balance, food intake, and nociception. In an experimental model of acute colitis, Hassani et al. [56] showed that lack of or inhibition of the NPY Y1 receptor makes the animals less susceptible to damage caused by colonic inflammation. Other studies of inflammatory processes in IBD highlight the role of neuronal NPY as a mediator of increased neuronal NOS (nNOS) and subsequent inflammation [57].

Conclusions

The enteric nervous system has a complex role in the small intestine, interacting with all cell types to modulate motility, secretion, pain perception, and inflammation (Fig. 1). Understanding the receptors and signal transduction pathways involved in mediating these functions can aid in the development of new therapeutic targets.

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Figure 1.

Role of enteric neurons in the small intestine: summary of the mechanisms of enteric neuronal modulation of peristalsis, secretion, pain perception, and inflammation in the small intestine. A—adenosine; Ach—acetylcholine; CB—cannabinoid; COX-2—cyclo-oxygenase-2; ECC—enterochromaffin cell; GLP—glucagon-like peptide-1; H₂S—hydrogen sulfide; NO—nitric oxide; NPY—neuropeptide Y; SP—substance P; TRPV1—transient receptor potential vanilloid type I; VIP—vasoactive intestinal peptide.

Table 1

Summary of new IBS drugs

Agent	Mechanism of action	Indication
Renzapride	5-HT ₃ antagonist and 5-HT ₄ agonist	IBS constipation
Cilansetron	5-HT ₃ antagonist	IBS diarrhea
Ramosetron	5-HT ₃ antagonist	IBS diarrhea
Prucalopride	5-HT ₄ agonist	IBS constipation
ME3412	Partial 5-HT ₃ agonists	IBS diarrhea
Linaclotid	Guanylate cyclase activator	CIC and IBS constipation
ROSE-010	GLP-1 analogues	IBS pain attacks
Lubiprostone	Type-2 chloride channel activator	CIC and IBS constipation
PMG51749	TRVP1 antagonist	Hypersensitivity in IBS
AMG517	TRVP1 antagonist	Hypersensitivity in IBS

CIC—chronic idiopathic constipation; GLP-1—glucagon-like peptide-1; IBS—irritable bowel disease; TRVP1—transient receptor potential vanilloid type I.

Table 2

Effects of ENS neurotransmitters on secretion

Inhibitory	Stimulatory
Adrenergic α_2	Adrenergic β
5-HT ₄	5-HT ₃
Purinergic P _{2y}	Nicotinic
Adenosine A	Muscarinic M ₃
GABA	
Histamine H ₃	
VIP	
Somatostatin	

GABA— γ -aminobutyric acid; VIP—vasoactive intestinal peptide.