

The enteric nervous system in physiological and pathological conditions

Tadeusz Kuder¹, Ilona Klejbor¹, Grzegorz Wróbel²

¹Department of Anatomy, *Collegium Medicum*, Jan Kochanowski University, Kielce, Poland

²Department of Clinical and Experimental Pathomorphology with Histology and Forensic Medicine Laboratory, *Collegium Medicum*, Jan Kochanowski University, Kielce, Poland

Medical Studies 2025; 41 (2): 65–74

DOI: <https://doi.org/10.5114/ms.2025.152424>

Key words: enteric nervous system, neurons, glial cells, interstitial cells of Cajal.

Abstract

The enteric nervous system is a specific part of the autonomic nervous system, whose role is mainly concerned with ensuring the proper functioning of the gastrointestinal tract. Numerous scientific studies show that the enteric nervous system plays many roles: it is responsible for peristalsis of the gastrointestinal tract, controls gastric acid secretion, regulates fluid permeation through the lining epithelium, controls local blood flow, and interacts with the immune and endocrine systems of the gut. Enteric nervous system failure or dysfunction can cause a number of intestinal neuropathies. These can be congenital or acquired neuropathies including those accompanying other conditions such as gastroparesis, achalasia, Crohn's disease, Chagas disease and many others, including neurodegenerative diseases. This article is a review of the literature and provides a comprehensive study of the enteric nervous system in normal conditions and numerous clinical conditions.

Introduction

The enteric nervous system (ENS), a specific part of the autonomic nervous system [1–3], is a complex, extensive structure consisting in humans of approximately 400–600 million neurons. These form a range of morphological and functional groups organized in a plexiganglionic system located in the walls of the digestive tract from the esophagus to the anal canal. The level of development of the ENS varies with the section of the digestive tract; it is most strongly developed in the small and large intestines, and in the plexuses of the muscular membrane (such as Auerbach's plexus) and of the submucosa (such as Meissner's plexus). It is slightly less developed in other parts. The ENS is connected to the central nervous system (CNS) through the vagus nerve and the thoracolumbar and lumbosacral nerves [2, 4, 5].

The enteric system fulfils a range of complex roles – peristaltic, secretory, and immunological – while also regulating local blood flow. This system is supported by peripheral glial cells, the so-called enteric glia, which assist the ENS in maintaining epithelial barrier integrity, regulating intestinal inflammation, and interacting with the intestinal microbiota [2, 4, 6].

It is known how important the role of the ENS is in the correct functioning of the digestive system and in its disease states, which include irritable bowel syndrome, slow transit constipation, gastroparesis, and short bowel syndrome [6, 7]. It therefore seems

appropriate to present an up-to-date review of the literature on both the general structure and function of the ENS in normal conditions, as well as its role in various pathological conditions.

History of ENS research

The structures of the intestinal plexuses were known in the nineteenth century and were named then by Georg Meissner and Leopold Auerbach. In 1899, Bayliss and Starling described the functions of these plexuses and presented the so-called “law of the intestine”, which describes the peristaltic abilities of the ENS, independent of the CNS. The operation of this law was noted again by Trendelenburg in a completely isolated guinea pig intestine [2, 7]. At the same time, Dogiel and Cajal drew up the first classification of the neurons found in the enteric plexuses. Over time, attention was drawn to the similarity of this part of the autonomic system to the brain. Robinson was the first to note this in 1907 [7]. In the 1960, Geoffrey Burnstock discovered that ENS neurons contain other neurotransmitters alongside noradrenaline (NA) and acetylcholine (ACh). This discovery initiated a series of studies of neurotransmission in the enteric nervous system. In 1995, Gershon demonstrated the presence of serotonin in ENS neurons [7]. Today, a number of cotransmitters and neuromodulators, including gaseous substances (NO and CO), are known to be present in the structures of the ENS [1, 6, 8].

Development of ENS structures

The development of the peripheral nervous system, including the intestinal system, begins in the fourth week of the prenatal period. ENS neurons (as well as enteric glia) migrate to the periphery from the neural crests. The population of precursor cells migrating to the esophagus and gastric cardia originates from the trunk segments of the neural crest. In turn, neuroblasts for the intestines come mainly from somites 1–7, which also serve as the sources for the vagus nerve. A small number of neuroblasts originate from the sacral section of the neural crests (behind the twenty-fourth somite): these neuroblasts mainly inhabit the lower part of the large intestine. Genetic labeling studies have shown that precursor cells migrate in waves, along specific paths, before the descending nerve fibers, and particularly the vagus nerve [7, 9, 10]. The migration of neuroblasts takes place with the participation of many trophic factors. One of the most important factors is the glial cell line-derived neurotrophic factor (GDNF), produced by the intestinal mesenchyme. This binds to the $\alpha 1$ protein molecule and affects RET (Rearranged during Transfection), the precursor cell receptor. Mutation of the gene that encodes RET leads to Hirschsprung's disease [10]. Other factors that activate RET receptors include neurturin (NTN), artemin (ART), and persephin (PSP). Moreover, the Mash-1 transcriptional regulator, which is involved in the formation of the noradrenergic system, affects the differentiation of ENS neurons, mainly in the esophagus.

Some of the precursor cells of the intestinal system are subject to the action of neurotrophin 3 (NT-3) and endothelin 3 (ET-3). The SOX proteins, and particularly SOX-10, also indirectly play a role in the development of the ENS. The mutation of the gene responsible for SOX-10 may additionally contribute to the development of Hirschsprung's disease [1, 10].

Precursor cells originating from the vagal section of the neural crest migrate caudally in the intestine, giving rise to Auerbach's plexus. Some of these cells move into the intestinal tube, giving rise to Meissner's plexus. Some neuroblasts separate from the intestinal tube and reach the pancreatic bud, forming the future intrapancreatic ganglia [1, 5].

Morphology of the ENS

The entire structure of the intestinal nervous system is based on two ganglia-containing plexuses: the muscular membrane of the intestine, i.e., Auerbach's plexus, and the mucous membrane, i.e., Meissner's plexus [2, 7, 8]. Auerbach's plexus (the myenteric plexus) mainly contains neurons responsible for motor activity and control of enzyme release from adjacent organs, while Meissner's plexus (the submucosal plexus) mainly contains sensory cells that transmit in-

formation to muscle neurons, as well as neurons and motor fibers that stimulate the secretion of crypt epithelial cells into the intestinal lumen. The submucosal plexus in humans consists of two parts: the internal part, located near the muscular layer of the mucosa, and the external part, also known as Schabadasch's plexus, located more peripherally, next to the circular muscular layer of the intestinal muscular membrane.

Parasympathetic fibers reach the plexuses via the vagus nerves (Figure 1). As studies employing retrograde transport show, a significant number of the nerve fibers contained in the X nerve that reach the lower part of the esophagus, stomach, and intestines come from the dorsal nucleus of the vagus nerve. In addition, a few fibers from the nucleus of the solitary tract and the nucleus ambiguus reach the entire gastrointestinal tract through this route [11, 12]. In addition to the "vagal" fibers, parasympathetic components also reach the large intestine via the pelvic nerves.

Preganglionic sympathetic neurons that innervate the stomach and intestines originate from the intermediate-lateral nuclei of the thoracic spinal cord; those for the stomach come from segments Th 6–9, those for the small intestine from segments Th 9–10, and those for the large intestine from Th 11–12 [12, 13]. Preganglionic sympathetic neurons send fibers first to the sympathetic ganglia of the abdominal cavity (visceral and mesenteric), and from these the postganglionic fibers depart to the digestive system. From the celiac ganglion they reach the stomach via the celiac trunk, and the duodenum and part of the jejunum via splanchnic nerves. The remaining part of the intestine receives sympathetic fibers from the superior and inferior mesenteric ganglion [11, 12].

Types of neurons in the ENS

The plexuses of the enteric system contain a number of groups of neurocytes that are differentiated both morphologically and functionally (Figure 1). To simplify the situation somewhat, there are five main groups of neurons: sensory intrinsic primary afferent neurons, interneurons, motor neurons, intestinofugal neurons, and interstitial neurons. ENS structures also contain glial cells [14].

Sensory intrinsic primary afferent neurons

Sensory innervation of the stomach and intestines comes from two sources: external and internal. The extrinsic sensory neurons originate from the sensory vagal ganglia and the sensory spinal ganglia. The intrinsic sensory neurons are located in both intestinal plexuses and are called intrinsic primary afferent neurons (IPANs). These occur in both the muscular and submucosal plexuses. Approximately 25% of all neurons in the submucosal plexuses are IPANs. They have a round or oval shape, a short axon, and

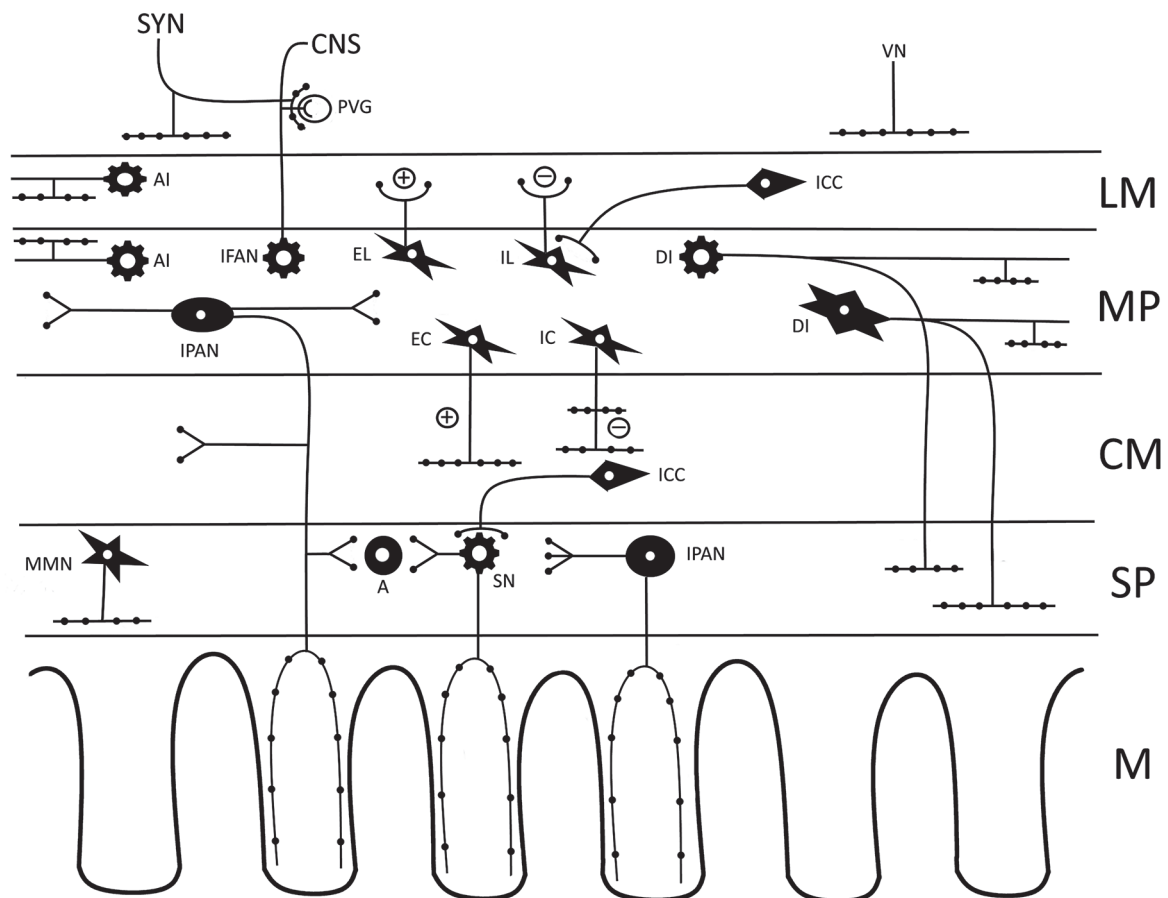


Figure 1. Location of ENS neurons and their types and interrelationships. (According to various authors)

A – arteriole, AI – ascending interneurons, CM – circular muscle, CNS – central nervous system, DI – descending interneurons, EC – excitatory circular muscle motor neurons, EL – excitatory longitudinal muscle motor neurons, IC – inhibitory circular muscular motor neurons, IL – inhibitory longitudinal muscle motor neurons, ICC – interstitial cells of Cajal, IFAN – intestino-fugal neurons, IPAN – intrinsic primary afferent neurons, LM – longitudinal muscle, M – mucosa, MP – myenteric plexus, MMN – mucosal motor neurons, PVG – prevertebral ganglia, SN – secretomotor neurons, SP – submucosal plexus, SYN – sympathetic nerves, VN – vagal nerve.

several longer dendrites; they are of type II in Dogiel's classification. IPAN neurons have three types of receptors: mechanoreceptors, thermoreceptors, and chemoreceptors. They form synaptic connections with interneurons and thus transfer information to ENS motor neurons. They participate in local reflexes that regulate fluid secretion, intestinal peristalsis, and the circulation of blood and lymph. They also react with intestinal cells of the endocrine and immune systems. Sensory IPANs use various neurotransmitters: those in the myenteric plexus mainly employ substance P (SP), while those in the submucosal plexus use tachykinins, including both SP and ACh. Most are also immunoreactive to calbindin [1, 15, 16].

Interneurons

Interneurons are neurons that mediate the transmission of stimuli from the IPAN sensory neurons

to the motor neurons. They are located mainly in the plexuses of the muscle membrane and are generally type I neurons in Dogiel's classification, having long axons and a number of short dendrites. A few interneurons are of Dogiel type III, having long axons and a few not very long dendrites. These fall into two groups, depending on the direction of conduction: ascending interneurons (conducting orally) and descending interneurons (conducting caudally). Ascending interneurons make synaptic contact only with neurons of the muscular ganglia, while descending interneurons form synaptic connections with motor neurons of both the submucosal plexus and the myenteric plexus. Most of the input to the ascending interneurons comes from IPANs, while only some comes from other ascending interneurons. In contrast, descending interneurons receive very little input from IPAN cells and much more input from other descending interneurons. Descending interneurons are therefore believed

to be strongly involved in the migrating myoelectric complex (MMC) of the small intestine [2, 15, 17, 18].

The main neurotransmitters of interneurons are ACh and somatostatin (SOM). The ascending group includes a few cholinergic neurons, while the descending group has many. A number of specific substances act as cotransmitters of intermediary neurons: serotonin (5-HT), nitric oxide (NO), vasoactive intestinal peptide (VIP), calcitonin gene related peptide (CGRP), dynorphin (DYN), γ -aminobutyric acid (GABA), neuropeptide Y (NPY), and ATP [1, 2, 14].

Motor neurons

ENS motor neurons innervate muscle layers, the walls of the internal arterioles, and the intestinal epithelium, including secretomotor and endocrine cells. Morphologically, they are classified as Dogiel type I neurons. Functionally, they may be either excitatory or inhibitory neurons, similarly to the interneurons that conduct towards the oral cavity (the ascending interneurons) and those that conduct in the caudal direction (the descending interneurons). They are divided by origin into extrinsic neurons (sympathetic and parasympathetic) and intrinsic neurons [1, 17]. Motor neurons can be divided into a number of groups by their target sites:

1. Neurons supplying the longitudinal muscles (excitatory and inhibitory)
2. Neurons supplying circular muscles (excitatory and inhibitory)
3. Neurons supplying the muscular layer of the mucosa (excitatory and inhibitory)
4. Neurons innervating entero-endocrine cells
5. Neurons innervating HCl-secreting cells (only in the stomach)
6. Cholinergic secretomotor/vasodilator neurons
7. Noncholinergic secretomotor/vasodilator neurons
8. Nonvasodilator secretomotor neurons

Types 1 to 5 are located in the muscular ganglia, while the remaining groups of neurons are found in the submucosal ganglia. Muscle motor neurons are responsible for mixing food with digestive enzymes, stomach emptying, and intestinal peristaltic movements. The peristaltic wave runs in the caudal direction, which is the result of the fact that inhibitory motor neurons (which relax intestinal contraction) direct the passage of food. Under normal conditions, inhibitory motor neurons conduct stimuli in the caudal direction, not the oral direction. Sometimes the direction of passage may be reversed, causing vomiting. The main neurotransmitters for excitatory motor neurons are ACh and SP (conditional opioids), while those for inhibitory motor neurons are NO, VIP, ATP, pituitary adenylate cyclase activating peptide (PACAP), GABA, and NPY [1, 18].

Abnormal stimulation or inhibition of the autonomic system leads to disorders in the functioning of the di-

gestive tract, such as when the sympathetic part inhibits the release of ACh and other neurotransmitters [2].

The secretomotor and endocrinomotor neurons are located mainly in the submucosal plexuses. The main function of the secretomotor neurons, both cholinergic and noncholinergic, is to secrete chloride ions into the intestinal lumen, drawing water molecules with them. The noncholinergic type uses VIP or a related peptide as its primary neurotransmitter, while the cholinergic type uses ACh and acts on muscarinic receptors in the intestinal mucosa.

Vascular secretomotor neurons regulate blood flow in the walls of the gastrointestinal tract and use either ACh or VIP and NPY, as the main neurotransmitter.

The main neurotransmitters of enteroendocrine cells are cholecystokinin (CCK), secretin, SOM, 5-HT, gastrin, and glucagon-like peptide-2 (GLP-2) [2, 19, 20]. GLP-2 plays an important role in glucose transport [21].

Intestinofugal neurons

Intestinofugal neurons (IFANs) are a subset of neurons located primarily in the ganglia of the myenteric plexus, which send their nerve fibers to ganglia outside the ENS (usually the sympathetic prevertebral ganglia: the splanchnic or mesenteric ganglia) [16, 17]. There are varying numbers of IFAN neurons in the individual parts of the gastrointestinal tract; most are located in the final section of the digestive tract. They receive stimulation in two ways: through mechanoreceptors that are sensitive to the stretching of the intestinal wall and through sensory neurons that form synapses with IFAN cells. Intestinofugal neurons are thus not primary neurons, and somewhat resemble interneurons in this respect. They are of type I or type II by Dogiel's classification.

The main neurotransmitter in IFAN neurons is ACh, while the cotransmitters are calbindin (CALB), SGRP, NO, and VIP [1, 16].

Intestinofugal neurons participate in entero-enteric reflexes that bypass the CSN and involve transmitting information from the large intestine to the small intestine, and vice versa. Their activation leads to weakened intestinal motility and reduced gastric secretion. IFAN neurons function as slowly adapting mechanoreceptors that detect changes in intestinal volume [16].

IFAN cells are arranged parallel to the circular muscular layer and respond to stretching of the intestinal wall, rather than to tension. When activated by colonic distension, they release ACh in the mesenteric ganglia and evoke fast excitatory postsynaptic potentials that are amplified by the parallel release of VIP. GABA is released in prevertebral ganglionic neurons, in turn facilitating the release of ACh from cholinergic IFAN neurons. This recurrent arc formed by IFANs and sympathetic neurons of the prevertebral ganglia provides a protective buffer against large increases in intravascular voltage and pressure [22].

Interstitial cells of Cajal

Interstitial cells of Cajal (ICC) are found within the myenteric plexus, both in the ganglia and inside the muscles. They are located between nerve endings and muscle cells [7]. These cells can act as “pacemakers” that generate a slow-wave contraction of smooth muscle due to the lack of unique ionic mechanisms in smooth muscle cells. In addition, the interstitial cells of Cajal participate in the neurotransmission process between nerve and muscle cells, and also create connections between themselves.

They are characterized by an elongated, spindle-shaped body with several protrusions. They have receptors for tachykinins and NO, produced by excitatory and inhibitory neurons, respectively, as well as for 5-HT [23]. As research has shown, these are cells of mesenchymal origin [2].

ENS glial cells

Neurons of the intestinal system are accompanied by numerous glial cells. Enteric glial cells are essential for the autonomous control of gastrointestinal homeostasis by the ENS [24], and they are thought to be two to three times more numerous than all other ENS cells combined [2]. Glial cells resemble brain astrocytes. They produce interleukins and are involved in intestinal inflammation. In Parkinson's disease, amyloid aggregations appear in ENS glial cells as they do in brain glial cells. In both cases, disorders of intestinal peristalsis also occur, which is associated with damage to glial cells. Glial cell damage has also been found in Crohn's disease and necrotic enteritis. A unique feature of ENS glial cells is the presence of glial fibrillary acidic protein (GFAP) in the cytoplasm [24]. They have a much more irregular shape than classic Schwann cells, with numerous protrusions forming “feet”. There is some evidence to suggest that enteric glia may have a neurosecretory function, affecting enterocytes and enteroendocrine cells [1, 2, 25–29].

Also interesting is the fact that nerve fibers in the ENS are surrounded only by glia, without collagen. This is typical of peripheral nerve fibers, including those of the sympathetic and parasympathetic systems [7, 26].

A diagram of the distribution of the different types of ENS cells is shown in Figure 1.

ENS and diseases

As previously emphasized, the enteric nervous system plays many roles: it is responsible for gastrointestinal peristalsis, it controls the secretion of gastric acid, it regulates the passage of fluids through the epithelium lining, it controls local blood flow, and it interacts with the intestinal immune and hormonal systems. Neurons of the ENS, together with glial cells, also contribute to maintaining the integrity of the ep-

ithelial barrier between the intestinal lumen and the cells and tissues within the intestinal wall. Failure or disturbances in the functioning of the ENS may thus lead to a number of enteric neuropathies [27]. These include congenital and acquired neuropathies, as well as those that accompany other disease states. They may also be iatrogenic or drug-induced [8].

Neuropathies associated with ENS dysfunction include achalasia, gastroparesis, Crohn's disease, Chagas disease, diabetes, slow-onset constipation, short bowel syndrome, Hirschsprung's disease, and some forms of colorectal cancer.

Achalasia

Achalasia refers to the impaired relaxation of the lower esophageal sphincter and weakened motility of the middle part of the esophagus. It results in dysphagia, food intolerance, and pneumonia [30, 31]. The exact causes of this disease are not fully explained, although it is known that the loss of inhibitory neurons of the myenteric plexus, with NO as a transmitter, results in the failure of the lower esophageal sphincter [2, 8, 32–34].

Gastroparesis

Gastroparesis is a set of clinical symptoms causing chronically delayed gastric emptying. The condition is caused by a reduction in the number of ENS neurons and a disruption in the functioning of motor neurons in the stomach wall. These issues may be post-surgical in origin, or may be associated with diabetes or other disorders in the functioning of the ENS. Sometimes drugs can cause gastroparesis, but most cases are idiopathic [35].

As biopsies show, gastroparesis involves a marked reduction in the number of interstitial cells of Cajal and of neuronal fibers in the circular muscle layer of the ENS structures. It has been suggested that gastroparesis may be caused by macrophages [36].

Gastroparesis can also result from other disorders, including a wide range of systemic, metabolic, and organic diseases such as collagen vascular diseases, neurological disorders, and paraneoplastic disorders caused by tumor-derived autoantibodies. Hereditary causes of gastroparesis have also been suggested, such as it being a result of recessive mutations in important mitochondrial genes, as in intestinal insufficiency syndrome [37–39].

Crohn's disease

Crohn's disease is an intestinal dysfunction with a broad clinical spectrum and four major subtypes (diarrheic IBS, constipation IBS, mixed IBS, and atypical IBS). The etiology of this disease is not fully understood, but genetic, environmental and immunological factors seem to be of equal importance [40].

Patients with this disease show hypertrophy of nerve fibers and hyperplasia in the mucosa and submucosal plexus, together with infiltration of inflammatory cells and neuromatous changes [29, 37]. Inflammation causes increased excitability in IPAN neurons, interneurons, and some motor neurons. One line of intestinal defense against inflammation is the increased production of the neurotransmitter VIP in the neurons of both intestinal plexuses [33]. This is an effective anti-inflammatory tactic as it affects ENS glial cells and induces the secretion of anti-inflammatory cytokines (interleukins), which protect the intestinal epithelium. In Crohn's disease, increased secretion of SP, NO, and pituitary adenylyl cyclase activating peptide (PACAP) is also observed in the neurons of the submucosa and muscle spots. On the other hand, the number of nerve fibers containing the peptide encoded by the calcitonin gene (CGRP) tends to be lower [1, 37, 41].

Chagas disease

Chagas disease, caused by the protozoan *Trypanosoma cruzi*, causes changes in multiple organs, which include cardiac hypertrophy and gastrointestinal symptoms. Changes in the gastrointestinal tract cause dilatation of the esophagus (megaesophagus) and are manifested by dysphagia, regurgitation of food, and sometimes aspiration of gastric contents into the respiratory system, which may consequently lead to aspiration pneumonia. Chagas disease results in disorders of intestinal motility that manifest as long-term constipation and pathological enlargement of the large intestine (megacolon). Neurodegeneration of ENS cells is observed, both in the ganglia of the myenteric plexus and the submucosa. A reduction in the number of ENS motor neurons, sometimes by as much as 50%, causes peristaltic disorders in the stomach and intestines, and particularly the large intestine. Intestinal hypersensitivity to ACh is also observed. NO is probably responsible for the changes in the intestinal mucosa and motility in this disease, as increased expression of nitric oxide synthetase (NOS) is observed [1, 2, 42].

Diabetes

A number of digestive system symptoms occur in both type-1 and type-2 diabetes; these include nausea, flatulence, diarrhea, and constipation. These symptoms result from diabetic neuropathy, including the death of ENS neurons in both the plexus of the muscular membrane and that of the submucosa. Subpopulations of enteric neurons prove to respond differently to diabetes, with some showing degeneration, others undergoing changes in neurotransmitter content without degeneration, and some remaining intact. The neurons that are most susceptible to apoptosis are inhibitory neurons containing nitric oxide (NO), VIP, NPY, and serotonin as neurotransmitters [33]. Reduced CGRP se-

cretion is similarly observed. Excitatory neurons with ACh and SP are affected the least [1, 43].

It should be noted that inhibitory neurotransmitters (NO, VIP, and GAL) seem to reduce their activity in early diabetes and increase in its later stages, probably as a result of regeneration.

Animal model studies have shown that the density of cholinergic innervation increases in diabetes in the jejunum, ileum, and the lamina muscularis of the duodenum [44, 45].

Serotonin is an important enteric neurotransmitter responsible for mediating migratory motor complex (MMC) contractions, or postprandial contractions, which are commonly impaired in diabetes [43].

Nerve growth factors and antioxidants may partially alleviate neuronal degeneration by inhibiting oxidative stress. It appears that transplantation of enteric neurons in diabetes would help restore the neuronal loss seen in severe enteric diabetes. This may be a potential future therapeutic option.

Research into the regulation of the expression of intestinal peptides by cytokines may also open up new possibilities for diabetes treatment [43].

Slow-onset constipation

The symptoms of slow-onset constipation, in addition to the constipation itself, also include nausea, abdominal pain, vomiting, and flatulence. Persistent constipation is the result of slow transit through the colon. Although the etiology of this disease is not entirely clear, it is associated with disorders of the ENS and of its connections with endocrine cells [2, 46]. Patients with slow-onset constipation show reduced numbers of mesenteric plexus neurons and interstitial Cajal cells [46]. Serotonin receptor antagonists exert their prokinetic effects by binding to their receptors on ENS motor neurons, leading to the release of ACh and other excitatory mediators. This group of substances includes prucalopride, which also has a neuroprotective effect on the enteric nervous system [47].

Short bowel syndrome

Short bowel syndrome is a condition where part of the small intestine has been surgically removed, e.g., due to cancer surgery or other damage. It can also involve congenital intestinal defects. In such cases, the body cannot absorb sufficient nutrients from food because part of the small intestine is missing or damaged. This condition naturally also involves a neuronal deficit in the ENS, with all its consequences.

The use of glucanin-like peptide 2 (GLP-2) can bring many benefits to patients affected by this condition. The mechanism of action is as follows: GLP-2 causes expansion of the epithelium of the small and large intestine mucosa and exerts antiapoptotic effects in both the normal and injured intestine. This occurs

through the expression of cell survival genes and proteins and by increasing intestinal blood flow [2, 48].

Hirschsprung's disease

Hirschsprung's disease is a congenital functional disorder of gastrointestinal motility caused by the absence of ganglia (aganglionosis) in the enteric nervous system. Ganglia are typically absent from the final section of the large intestine (sigmoid colon and rectum) [10, 33], causing narrowing of the damaged section of the intestine and widening of the section immediately before the narrowing.

Aganglionosis always affects the anus and extends proximally for a variable distance and affects both the myenteric plexus and the submucosal plexus. This results in reduced motility and intestinal function, or even its complete absence [33].

As mentioned earlier, primary intestinal ganglion cells originate from the neural crest and migrate into the GI tract from the proximal to distal end by week 13, after which they differentiate into mature ganglion cells. In infants with Hirschsprung's disease, this migration and the subsequent differentiation are impaired or incomplete due to a mechanism that has not yet been elucidated. The most common theory is that neural crest cells never reach the distal gut because they mature or differentiate earlier than they should. Another view is that normal neuronal migration occurs, but that the precursor cells in the distal intestine fail to survive and differentiate [8, 49]. It seems, however, that the most likely cause of the disorders is multifactorial, and includes genetic causes. It is known that mutation of the SOX protein, which indirectly affects the development of ENS, is a factor in the development of Hirschsprung's disease [50, 51].

Certain forms of colon cancer

Invasion by cancer of the digestive system, and particularly of the large intestine, can destroy both the intestinal tissue and the nerve fibers and neurons of the local ENS, resulting in the atrophy of the submucosal and muscular plexuses within the tumor and in areas adjacent to it [8]. This reduction in the size of the plexuses is accompanied by an increased number of galanin-immunoreactive neurons and thus increased GAL content in parts of the colon located near the tumor. As is well known, galanin is a neuroprotective peptide that can inhibit apoptosis, and thus promote the survival of cancer cells [52]. Changes have also been observed in the components of the submucosal and musculoskeletal plexuses located near the tumor foci. These changes include reductions in the number of neurons and nerve fibers containing the neuropeptides VIP, PACAP, NPY, SOM, SP, and CGRP [53, 54]. Additionally, there turn out to be numerous other interactions between ENS neurons, cancer cells, and other cell

types present in the colon wall, which increase the invasiveness of cancer cells and have a negative impact on the course of the disease [52, 55].

ENS in neurodegenerative diseases

Progressive neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis, lead to changes in neurons in certain brain regions that affect body motor skills. It was observed over three decades ago that these diseases also cause a number of changes in the intestinal nervous system. For example, in Parkinson's disease, there is a loss of dopaminergic neurons in the ENS in both plexuses, and Leve bodies are also observed [33, 56–58].

As the research of Singaram *et al.* [59] has shown, a ten-fold decrease in the number of dopaminergic neurons can be observed in patients with Parkinson's disease who also underwent colon resection due to adenocarcinoma or chronic constipation. This decrease in the number of enteric neurons was associated with the presence of Lewy bodies in both dopaminergic and nondopaminergic mesenteric neurons [60].

ENS is thus a key modulator of intestinal barrier function and a regulator of intestinal homeostasis. A "leaky gut" acts as a gateway for the translocation of bacteria and toxins that can initiate downstream processes. Data indicate that changes in the gut microbiome in conjunction with an individual's genetic background can modify the ENS, CNS, and immune system, while impairing barrier function and contributing to a range of disorders, such as irritable bowel syndrome, inflammatory bowel disease, and neurodegeneration [61].

Research results from recent years have suggested that some neurotrophic factors, such as GDNF, may potentially be used as neuroprotective agents to prevent and treat the symptoms observed in the ENS during parkinsonism [62].

In Alzheimer's disease, β -amyloid deposits and dysfunction of cholinergic neurons are observed in midbrain neurons. As studies in transgenic mice have shown, the β -amyloid precursor is normally expressed in the ENS [60, 63] and is necessary for proper gastrointestinal motility, immunity, and secretion [64]. Approximately 70% of enteric neurons are cholinergic, which means that potential pathophysiological effects of Alzheimer's disease on the ENS may be significant [8].

Studies of the human ENS in Alzheimer's disease have been sporadic. Immunoreactive β -amyloid plaques were reported in the intestinal submucosa of 2 patients [65].

Some studies, including those looking at amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), have found prion promoters in ENS neurons, and not only in the central and peripheral nervous system. This results in the loss of motor neu-

rons and their processes, and thus in disorders of gastrointestinal transit [66–68].

Conclusions

The enteric nervous system is a very important part of the autonomic nervous system, and one which resembles the central nervous system in both its components and functions. The ENS is responsible for the motility of the digestive system, the secretion of digestive enzymes, and the absorption of nutrients. In addition, it has an immunological and regulatory function in relation of local blood flow. This system is supported by the so-called enteric glia, which assist the ENS in maintaining epithelial barrier integrity, in controlling intestinal inflammation, and in interacting with the intestinal microbiota. Its key roles involve both normal conditions and various inflammatory and functional intestinal diseases and intestinal neuropathies, including Hirschsprung's disease. Its function is also important in neurodegenerative diseases, including not only Alzheimer's disease, but also Parkinson's disease and neurodevelopmental disorders. The ENS is a key modulator of intestinal barrier function and a regulator of intestinal homeostasis. Many diseases of the digestive system thus have a broad context, and are usually related to the improper functioning of the intestinal nervous system.

Funding

Project No. SUPB.RN.24.014

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

- Arciszewski MB, Zacharko-Siembida A. Układ nerwowy jelitowy. *Novae Res Gdynia*. 2008.
- Fleming MA, Ehsan L, Moore SR, Levin DE. The enteric nervous system and its emerging role as a therapeutic target. *Gastroenterol Res Pract*. 2020; 2020: 8024171.
- Kuder T. Autonomiczny układ nerwowy. Wyd. AS, Kielce, 2002.
- Fung C, Vanden Berghe P. Functional circuitry and signal processing in the enteric nervous system. *Cell Mol Life Sci*. 2020; 77: 4505-4522.
- Costa M, Glise H, Sjødahl T. The enteric nervous system in health and disease. *Gut*. 2001; 47 (suppl 4): IV1.
- Schemann M, Neunlist M. The human enteric nervous system. *Neurogastroenterol Motil*. 2004; 16: 55-59.
- Gershon MD. The enteric nervous system: a second brain. *Hosp Pract*. 1995; 34: 31-46.
- Furness JB. The enteric nervous system and neurogastroenterology. *Nat Rev Gastroenterol Hepatol*. 2012; 9: 286-294.
- Gershon MD. Genes and lineages in the formation of the enteric nervous system. *Cur Opin Neurobiol*. 1997; 7: 101-109.
- Gershon MD. Development of the enteric nervous system (ENS). In: Hirschsprung's Disease and Allied Disorders. Puri P, Rolle U (eds.). Springer, Berlin 2007.
- Schemann M, Grundy D. Electrophysiological identification of vagal innervated enteric neurons in guinea pig stomach. *Am J Physiol*. 1992; 263: 709-718.
- Olsson C, Chen BU, Jones S, Chatway TK, Costa M, Brookes SJH. Comparison of extrinsic afferent innervation of guinea pig distal colon and rectum. *J Comp Neurol*. 2006; 496: 787-801.
- Furness JB, Costa M. The adrenergic innervation of the gastrointestinal tract. *Ergeb Physiol*. 1974; 69: 2-51.
- Furness JB. Types of neurons in the enteric nervous system. *J Auton Nerv Syst*. 2000; 81: 87-96.
- Furness JB, Jones C, Nurgali K, Clerc N. Intrinsic primary afferent neurons and nerve circuits within the intestine. *Prog Neurobiol*. 2004; 72: 143-164.
- Furness JB. Novel gut afferents: Intrinsic afferent neurons and intestinofugal neurons. *Auton Neurosci*. 2006; 125: 81-85.
- Furness JB, Calaghan BC, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. In: *Microbial Endocrinology: The microbiota – Gut Brain Axis in Health and Disease*. Lyte M, Cyran JF (eds.). Springer, New York 2014.
- Kunze WA, Furness JB. The enteric nervous system and regulation of intestinal motility. *Ann Rev Physiol*. 1999; 61: 117-142.
- Hansen MB. The enteric nervous system I: organisation and classification. *Pharmacol Toxicol*. 2003; 92: 105-113.
- Hansen MB. The enteric nervous system II: Gastrointestinal functions. *Pharmacol Toxicol*. 2003; 92: 249-257.
- Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, Daly K, Maillet EL, Nionomiya Y, Mosinger B, Sirazi-Beechey SP. T1R3 and gustducin in gut sense sugars to regulate expression of Na⁺-glucose cotransporter 1. *Proc Natl Acad Sci USA*. 2007; 104: 15075-15080.
- Szurszewski JH, Ermilow LG, Miller SM. Prevertebral ganglia and intestinofugal afferent neurones. *Gut*. 2002; 1 Suppl: 6-10.
- Wouters MM, Farrugia G, Schemann M. 5-HT receptors on interstitial cells of Cajal, smooth muscle and enteric nerves. *Neurogastroenterol Motil*. 2007; 19, Supl. 2: 5-12.
- Boesmans W, Lasrado R, Vanden Berghe PV, Pachnis V. Heterogeneity and phenotypic plasticity of glial cells in the mammalian enteric nervous system. *Glia*. 2015; 63: 229-241.
- Gabella G. Fine structure of the myenteric plexus in the guinea-pig ileum. *J Anat*. 1972; 111: 69-97.
- Gabella G, Trigg P. Size of neurons and glial cells in the enteric ganglia of mice, guinea-pigs, rabbits and sheep. *J Neurocytol*. 1984; 13: 49-71.
- Sharkey KA. Emerging roles for enteric glia in gastrointestinal disorders. *J Clin Invest*. 2015; 125: 918-925.
- Grubisic V, Gulbensen D. Enteric glia: the most alimentary of all glia. *J Physiol*. 2017; 595: 557-570.
- Spencer NJ, Costa M, Briele J ST (ed.). Springer, 2022.
- Boeckstaens GE, Zaninotto G, Richter JE. Achalasia. *Lancet*. 2014; 383: 83-93.
- Schlottmann F, Neto RML, Herbella FAM, Patti MG. Esophageal achalasia: pathophysiology, clinical presentation, and diagnostic evaluation. *Am Surg*. 2018; 84: 467-472.

32. Ates F, Vaezi MF. The pathogenesis and management of achalasia: current status and future directions. *Gut Liv*. 2015; 9: 449-463.
33. Schemann M, Neunlist M. The human enteric nervous system. *Neurogastroenterol Motilit*. 2004; 16 Suppl 1: 55-59.
34. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Intraspinal botulinum toxin for the treatment of achalasia. *N Engl J Med*. 1995; 332: 774-778.
35. Grover M, Farrugia G, Stanghellini V. Gastroparesis: a turning point in understanding and treatment. *Gut*. 2019; 68: 2238-2250.
36. Pasricha PJ, Grover M, Yates KP, Abell TL, Bernard CE, Koch KL, McCallum RW, Sarosiek I, Kuo B, Bulat R, Chen J, Shulman R, Lee L, Tonascia J, Miriel LA, Hamilton F, Farrugia G, Parkman HP. Functional dyspepsia and gastroparesis in tertiary care are interchangeable syndromes with common clinical and pathological features. *Gastroenterology*. 2021; 160: 2006-2017.
37. Holland AM, Bon Frauches AC, Keszthelyi D, Melotte V, Boesmans W. The enteric nervous system in gastrointestinal disease etiology. *Cell Mol Life Sci*. 2021; 78: 4713-4733.
38. Hunter MF, Peters H, Salemi R, Thorburn D, Mackay MT. Alpers syndrome with mutations in POLG: clinical and investigative features. *Pediatr Neurol*. 2011; 45: 311-318.
39. Thorson W, Diaz-Horta O, Foster J 2nd, Spiliopoulos M, Quintero R, Farooq A, Blanton S, Tekin M. De novo ACTG2 mutations cause congenital distended bladder, microcolon, and intestinal hypoperistalsis. *Hum Genet*. 2014; 133: 737-742.
40. Gocel O, Pendrasik K, Frak W, Małeczka-Wojcieszko E. Genetic polymorphisms in the pathogenesis and course of Crohn's disease. *Medical Studies*. 2023; 39: 396-404.
41. Seillet C, Luong K, Tellier J, Jacquilot N, Shen RD, Hickey P, Wimmer VC, Whitehead L, Rogers K, Smyth GK, Garnham AL, Ritchie ME, Belz GT. The neuropeptide VIP confers anticipatory mucosal immunity by regulating ILC3 activity. *Nature Immunol*. 2020; 21: 168-177.
42. Menchén L, Colón AL, Madrigal JL, Beltrán L, Botella S, Lizasoain I, Leza JC, Moro MA, Menchén P, Cos E. Activity of inducible and neuronal nitric oxide synthases in colonic mucosa predicts progression of ulcerative colitis. *Am J Gastroenterol*. 2004; 99: 1756-1764.
43. Chandrasekharan B, Srinivasan S. Diabetes and the enteric nervous system. *Neurogastroenterol Motil*. 2007; 19: 951-960.
44. Monckton G, Pehowich E. Autonomic neuropathy in the streptozotocin diabetic rat. *Can J Neurol Sci*. 1980; 7: 135-42.
45. Spangeus A, Suhr O, El-Salhy M. Diabetic state affects the innervation of gut in an animal model of human type 1 diabetes. *Histol Histopathol*. 2000; 15: 739-44.
46. El-Salhy M. Chronic idiopathic slow transit constipation: pathophysiology and management. *Colorectal Dis*. 2003; 5: 288-296.
47. Bianco F, Bonora E, Natarajan D, Vargiolu M, Thapar N, Torreson N, Giancola F, Boschetti E, Volta U, Bazzoli F, Mazoni M, Seri M, Clavenzani P, Stangelini V, Sternini C, De Giorgio R. Prucalopride exerts neuroprotection in human enteric neurons. *Am J Physiol Gastrointest Liver Physiol*. 2016; 310: G768-G775.
48. Drucker DJ, Erlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci USA*. 1996; 93: 911-916.
49. Swenson O. Hirschsprung's disease: a review. *Pediatrics*. 2002; 109: 914-918.
50. Bondurand N, Natarajan D, Barlow A, Thapar N, Pachnis V. Maintenance of mammalian enteric nervous system progenitors by SOX 10 and endothelin 3 signaling. *Development*. 2006; 133: 2075-2086.
51. Hong CS, Saint-Jeannet JP. Sox proteins and neural crest development. *Semin Cell Develop Biol*. 2005; 16: 694-703.
52. Godlewski J, Kmiec Z. Colorectal cancer invasion and atrophy of the enteric nervous system: potential feedback and impact on cancer progression. *Int J Mol Sci*. 2020; 21: 3391.
53. Godlewski J, Lakomy IM. Changes in vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide and neuropeptide Y-ergic structures of the enteric nervous system in the carcinoma of the human large intestine. *Folia Histochem Cytobiol*. 2010; 48: 208-216.
54. Godlewski J, Kalczyk J. Somatostatin, substance P and calcitonin gene-related peptide-positive intramural nerve structures of the human large intestine affected by carcinoma. *Folia Histochem Cytobiol*. 2010; 48: 475-483.
55. Rademakers G, Vaes N, Schonkeren S, Koch A, Sharkey KA, Melotte V. The role of enteric neurons in the development and progression of colorectal cancer. *Biochim Biophys Acta Rev Cancer*. 2017; 1868: 420-434.
56. Qualman SJ, Haupt HM, Yang P, Hamilton SR. Esophageal Lewy bodies associated with ganglion cell loss in achalasia. Similarity to Parkinson's disease. *Gastroenterology*. 1984; 87: 848-856.
57. Anderson G, Noorian AR, Taylor G, Anitha M, Bernhard D, Srinivasan S, Greene JG. Loss of enteric dopaminergic neurons and associated changes in colon motility in an MPTP mouse model of Parkinson's disease. *Exp Neurol*. 2007; 207: 4-12.
58. Kowalski K, Mulak A. Brain-gut microbiota axis in Alzheimer's disease. *J Neurogastroenterol Motil*. 2019; 25: 48-60.
59. Singaram C, Ashraf WA, Gaumnitz EA, Torbey C, Sengupta A, Pfeiffer R, Quigley EM. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. *Lancet*. 1995; 346: 861-864.
60. Rao M, Gershon MD. The bowel and beyond: the enteric nervous system in neurological disorders. *Nat Rev Gastroenterol Hepatol*. 2016; 13: 517-528.
61. Niesler B, Kuerten S, Demir IE, Schafer KH. Disorders of the enteric nervous system – a holistic view. *Nat Rev Gastroenterol Hepatol*. 2021; 18: 393-410.
62. Chalazonitis A, Rao M, Sulzer D. Similarities and differences between nigral and enteric dopaminergic neurons unravel distinctive involvement in Parkinson's disease. *NPJ Parkinson's Dis*. 2022; 8: 50.
63. Arai H, Lee VM, Messinger ML, Greenberg BD, Lower DE, Trojanowski JQ. Expression patterns of beta-amyloid precursor protein (β -APP) in neural and nonneural human tissues from Alzheimer's disease and control subjects. *Ann Neurol*. 1991; 30: 686-693.
64. Puig KL, Swigost AJ, Zhou X, Sens MA, Combs CK. Amyloid precursor protein expression modulates intestine immune phenotype. *J Neuroimmune Pharmacol*. 2012; 7: 215-230.
65. Joachim CL, Mori H, Selkoe DJ. Amyloid β -protein deposition in tissues other than brain in Alzheimer's disease. *Nature*. 1989; 341: 226-230.
66. Geser F, Martinez-Lage M, Kwong LK, Lee VM, Trojanowski JQ. Amyotrophic lateral sclerosis, frontotemporal dementia and beyond: the TDP-43 diseases. *J Neurol*. 2009; 256: 1205-1214.
67. Kabashi E, Valdmanis PN, Dion P, Spiegelman D, McConkey BJ, Velde CV, Bouchard JP, Lacomblez L, Pochigaeva K,

- Salachas F, Pradat PF, Camu W, Meninger V, Durpe N, Rouleau GA. TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. *Nat Genet.* 2008; 40: 572-574.
68. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey MC, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretschmar HA, Trojanowski JQ, Lee VM-Y. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science.* 2006; 314: 130-133.

Address for correspondence

Grzegorz Wróbel
Department of Clinical and
Experimental Pathomorphology with
Histology and Forensic Medicine Laboratory
Collegium Medicum
Jan Kochanowski University
Kielce, Poland
E-mail: grzegorz.wrobel@ujk.edu.pl

Received: 12.06.2024

Accepted: 6.09.2024

Online publication: 20.06.2025