Chapter

The Brain-Like Enteric Nervous System

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Abstract

Understanding the autonomic supply at the gastrointestinal tract is one of the significant challenges for science. Its complex network of neurons exists on a broad evolutionary scale, from Hydra to mammals, and in a higher number than those found in the vertebrate spinal cord. Inside the gastrointestinal tract, enteric neurons regulate several functions with intrinsic processes and communicate with the other complex known as the microbiome. Outside the gastrointestinal tract, the enteric neurons project to the brain stem and spinal cord via the gut–brain axis. Furthermore, this enteric system has close functional relationships with the immune system for a rapid response to unhealthy food. The present chapter focuses on the structure, function, and pathologies of the enteric nervous system.

Keywords: enteric nervous system, gastrointestinal, microbiome, brain–gut axis, second brain

1. Introduction

The enteric nervous system (ENS) is a complex network of neurons and glia that regulates the physiology of the gastrointestinal tract. It is the largest division of the autonomic nervous system and is responsible for controlling several functions, including motility, secretion, blood flow, and immune surveillance. The ENS spans the entire length of the gastrointestinal tract and comprises over 100 million neurons in humans, a higher number than those found in the spinal cord. It is considered a second brain because it carries out specific functions that do not depend on the central nervous system (CNS). From an evolutionary perspective, however, the ENS could be considered the first brain, as it evolved early in development in multicellular organisms to allow for efficient food processing and digestion. Although such a discussion is out of the scope of this chapter, it is worth saying that nutrients imposed an evolutionary pressure on all living species because it is a critical vital need; in animals, it was necessary to adapt a precise autonomic control, leading to the rise of a primitive system that became the ENS in contemporary species. Undoubtedly, this

later fact reveals that the ENS is the oldest region of the nervous system; the Hydra, for example, a 500 million years cnidarian [1], is the oldest known group with sensory neurons in the oral region to regulate feeding, and with clustered ganglion neurons at the hypostome-tentacle junction to trigger contraction burst pulses of the epithelium to allow movement and ingestion [2]. The organization of these neurons is of great significance since it persisted throughout evolution and is observed from Hydras up to humans [3].

The complex circuitry of the ENS allows for the organization of both local and long-distance reflexes. These reflexes start with sensory neurons that detect changes in the gut's environment, such as the presence of food, and then relay this information to the motor neurons that control gut function. At a glance, the ENS is an essential component of the autonomic nervous system, and its complex and sophisticated functions make it a critical player in regulating gastrointestinal function. Furthermore, its ability to function independently of the CNS, coupled with its communication with the brain, highlights the importance of this intricate neural network in maintaining overall health and well-being.

The autonomic control of the intestine was first described in 1847 by Robert Remak, who settled the basis for further descriptions by Georg Meissner (1852) and Leopold Auerbach (1862), establishing the initial studies about the ENS [4]. Now, data show that neurons and glia of the ENS have their embryological origin at the neural crest, and before and after arriving at the gastrointestinal tract, they differentiate into glia and different types of neurons [5]. A detailed analysis of cellular and molecular processes of ENS development is in an excellent review [6]. In brief, this system originates from neural crest cells (NCC) derived from the ectoderm at the neural tube. NCC delaminate, and during this epithelial-mesenchymal transition, other levels or axes of the neural tube arise, named cranial, cardiac, vagal, truncal, and sacral. Subsequently, they proliferate and migrate until colonize specific sites. In such a process, they differentiate into various types of cells to structure the tissues to make up the gastrointestinal tract [6, 7]. These tissues can be diverse: connective tissue, endocrine cells, glia, and enteric neurons. The process of cell differentiation is necessary for a functional ENS; hence it is gradual because markers for neuronal types appear and may continue to a particular postnatal stage [8]. Studies are increasing to determine which molecules are involved in cell differentiation, such as the transcription factors and signaling pathways. Many of these molecules are for neuronal differentiation, as the SRY-like high-mobility group (HMG)-box (Sox) family, Sox6, Sox10, Mash1 (now called Ascl1), Hand 2; and those known for glial differentiation, as the GDNF, Neurturin, and the signaling pathway Ret – Rearranged during transfection – Notch [9].

2. Neurons and glia

The neurons form at least two ganglionic nerve plexuses running along the submucose layer of the gastrointestinal tract, the inner and the outer submucose plexus, and even a third plexus observed in humans [10]. Also, they are called the myenteric or Auerbach's plexus, the submucous or Meissner's plexus, and the mucous plexus [11]. The first is a plexus that runs from the esophagus to the rectum, while the others are located mainly in the intestines, with some functions independent of the influence of the central nervous system [12]. Thus, the ENS is a specialized system with significant self-supporting processes.

There are different kinds of neurons in the ENS. In the 19th century, the Russian neuroscientist Alexandre S. Dogiel described three types of neurons at the ENS for the first time. The current terminology recognizes them as Type I (one axon and short dendrites), Type II (one axon and long dendrites), and Type III neurons (one axon and long tapering and branching dendrites found in the guinea pig); all of them also recognized as multipolar neurons [13]. Then, Type IV was described by Stach in the 1980s as a radiate multidendritic uniaxonal neuron with branches between the myenteric and submucous plexus [14], and Type V referring neurons with long dendrites observed in pigs and humans [15, 16].

The Dogiel Type II neurons in the guinea pig are primary afferent neurons [17] also found in humans in the stomach, small intestine, and colon [13]. The Dogiel Type I neurons show specific subdivisions depending on the shape; stubby neurons have short and stubby dendrites, spiny neurons with short and thorny dendrites, and hairy neurons with short and thin dendrites [13].

ENS glial cells outnumber neurons, as occurs in the central nervous system. They are flat and stellate-shaped, extended over neurons and neuronal processes, with a similar arrangement between vertebrate species [18]. The structure and molecular characteristics of enteric glia suggest that they are astrocytes-like cells [19] subdivided into Type I or protoplasmic glia, and Type II or fibrous glia, an organization determined by the microenvironment [20]. Also, there is a description of a Type III glia showing long and branched processes, and the Type IV referring to that glia on nerve fibers in the muscle layer; notwithstanding, a new proposal is to name them according to their location, cells in the myenteric and submucosal plexuses referred as EG_{MP} and EG_{SMP}, and cells in the mucosa and musculature as EG_{Mucosa} and EG_{IM} [21].

Although the classification of ENS neurons and glia is remarkable, as far as innovative methods become available, identifying and characterizing the structure of these cells will still be refined. The task will improve our understanding of gastrointestinal functions, diseases, and treatments.

3. Microbiome

The gastrointestinal microbiome (GM), previously known as the intestinal flora, is the world of microorganisms that live in the gut to support digestion and significantly impact health. It includes different bacterial taxonomic groups and their interrelations [22]; for example, 400+ bacterial species live just in the human colon [23]. No matter whether microbiomes also exist in the skin, mouth, or reproductive tract, GM is the most well-studied in humans. Thus, it is known that starting at birth, the GM is acquired from the mother during delivery and breastfeeding [24]. GM plays a significant role in breaking down food, extracting nutrients, and producing vitamins necessary for human health; consequently, it is modified during life depending on the environment of the subject [25]. Considering the complex ecosystem that several microbes species establish in the gut, the role they play for health, their physiology as a group that impacts health if modified, and the many functions that even affect behavior, the GM is considered an organ by itself [22, 26]. Such a statement is further consolidated due to the relationship between GM and ENS.

The afferent starting point is at the enteroendocrine cells within the gut. They are specialized cells that respond to ingested substances. Although not entirely known, they release hormones such as cholecystokinin to activate nerve pathways to the central nervous system [27]. Also, neurotransmitters such as the gamma-aminobutyric

acid (GABA) play a specific role in activating the afferent pathways [28]. Whatever the milieu chemicals, the activation of enteroendocrine cells, in turn, activates the two main types of ENS afferent neurons, the extrinsic and intrinsic afferents, which differ depending on the location of their cell bodies, outside (extrinsic) or inside (intrinsic) the ENS [29]. Notwithstanding, the exact mechanisms by which the GM activates the ENS are yet not completely understood, but it represents the first interface between intestinal content and ENS to activate the afferent pathways of the brain–gut axis [30].

4. Brain–gut axis

Gastrointestinal afferent neurons are Dogiel Type II cells representing about 20% of ENS neurons. The intrinsic complex is formed by the intrinsic primary afferent neurons (IPAN), interneurons, and motor neurons, which organize local circuits within the ENS to trigger CNS-independent reflexes that regulate several aspects of gut function [31]. The extrinsic neurons have cell bodies in the dorsal root ganglia and the complex jugular-nodose ganglia at the jugular foramen. Extrinsic fibers from the stomach and upper intestine run from the gut to the CNS via the vagus and splanchnic nerves, and those from the distal intestine run via pelvic nerves [32].

The jugular ganglion is the smallest afferent cluster of sensory neurons of the vagus nerve [33] and also has neurons with similar properties as small dorsal root ganglion neurons, suggesting a nociceptive role [34]. The afferents project to the brain stem, specifically to the nucleus of the solitary tract (NTS), area postrema, and the upper cervical dorsal horn [35]. The nodose ganglion and its neurons are organized in a viscerotopic position, i.e., located inside the ganglion, depending on the origin of the afferent information. Then, they project central fibers through the solitary tract that synapse on neurons of the NTS located in the medulla [36]. NTS is a complex nucleus with projections to different cortex areas and brain nuclei, such as the insular cortex, frontal cortex, or thalamus [37]. It is a region for inputs from several regions, such as the insular cortex, paraventricular nucleus, hypothalamus, and amygdala [38].

The cell bodies of splanchnic afferents neurons are in the dorsal roots ganglia of the thoracolumbar spinal cord. Such neurons activate ascendent fibers in the spinothalamic, spinoreticular, and dorsal column pathways that carry information about noxious stimuli to different parts of the CNS, where it is interpreted as pain or discomfort [39]. However, the information from splanchnic afferents has a less graded sensation in response to distention, implying more intense or unpleasant sensations than vagal and pelvic afferents [40].

Pelvic afferent neurons are the third input pathway critical in sending information from the gastrointestinal tract to the CNS. These neurons are subdivided into two types based on their firing pattern: tonic and phasic. Tonic afferents become active by colonic distention and mainly consist of unmyelinated C fibers, while phasic afferents discharge at the onset and cessation of distention and include myelinated A-delta fibers [41]. They enter the spinal cord through the lumbosacral dorsal root ganglia and activate different ascending tracts [42].

Activation of afferent pathways triggers the different reflexes of the gastrointestinal system. Intrinsic activity is represented by ascending and descending reflexes to increase the luminal content and initiate peristalsis [29]. Ascending reflexes are excitatory pathways that induce the peristaltic contraction of circular muscles, and

descending reflexes were described as inhibitory [43]. However, specific inhibitory and excitatory neurons exist in ascending and descending pathways [44]. These reflexes initiate following the enteroendocrine cell's activation of the IPANs, then activate interneuron and motor neurons to produce the appropriate response [45]. IPANs are located in submucosal or myenteric areas, and they respectively trigger peristaltic and secretory reflexes or stretch contraction reflexes via cholinergic pathways [46].

The extrinsic activity allows reflexes to perform tasks involving neurons in the CNS. Neurons at the dorsal motor nucleus of the vagus and at the NTS activate efferent pathways via the vagal outflow to the ENS [37]. Such pathways allow a fine modulation of gastrointestinal functions, mainly in the upper gastrointestinal tract, although the vago-vagal reflexes also include esophagogastric, gastrograstric, and duodenogastric reflexes that still need more studies [47]. It is noteworthy that vagal reflexes are not a fixed response, as observed in spinal reflexes. Instead, they are modulated, and the response depends on the demand of the gastrointestinal tract [48].

5. Immune system

A healthy gastrointestinal system depends on the immune system, notwithstanding it also depends on the collaborative work that immunity maintains with the microbiota and the ENS. The gastrointestinal tract is the region with more concentration of immune cells, mainly macrophages. The microbiota stimulates both macrophages and ENS neurons to synthesize and release, respectively, the bone morphogenic protein 2 (BMP2) and the colony stimulator factor 1 (CSF1). ENS neurons have receptors for BMP2 and macrophages for CSF1, representing the complex crosstalk signal circuit that exists to control gut function [49, 50].

Macrophages represent a diverse group of guard cells for the custody of the surrounding environment aimed to prevent infections [51]. Those in the smooth muscle of the gastrointestinal tract are in close contact with ENS neurons and regulate synaptic functions that include control of neuropeptides and neurotransmitters, but also receive activation from the ENS for the neuroimmune responses [52]. The comparison between lamina propia macrophages located in the epithelium close to the lumen, and those muscularis macrophages, show that they have particular responses to support the specialized interaction of the ENS and the immune system [53]. In the event of a response, such as inflammation, both macrophages and the ENS become active to restore homeostasis. Such activation is observed in local circuits but also in central ones as the inflammatory reflex, in which central neurons in the NTS and motor neurons of the dorsal nucleus of the vagus nerve become active [54].

6. Diseases

Several disorders are linked to dysfunctions of the ENS. For example, the so-called enteric neuropathies arise from the loss, degeneration, or functional impairment of enteric neurons, which may be congenital disabilities during development induced by infectious agents or conditions such as diabetes and neurodegenerative diseases [55]. Furthermore, specific dysfunctions or damage to the submucosal plexus are linked to gastrointestinal disorders and other disorders.

6.1 Irritable bowel syndrome (IBS)

According to the Rome IV criteria, the symptoms of IBS are frequent abdominal pain associated with bloating or the rhythm of evacuations, such as constipation, diarrhea, or both. Also, IBS is subdivided according to the defecation pattern, those with diarrhea IBS-D, constipation IBS-C, a mixed subtype IBS-M, and even those not yet subtyped, known as IBS-U [56]. Diagnosis includes the frequency criterion, i.e., if the abdominal pain occurs once a week, for at least 3 months, and the onset of symptoms with a minimum of six months before diagnosis [57]. IBS is recognized by altered gastrointestinal motility, characterized by accelerated GI transit in response to enteric ganglionitis in severe cases, carbohydrate malabsorption, bacterial overpopulation [58], visceral hypersensitivity, mucosal permeability, and altered microbiota [59].

The etiology of IBS has not yet been fully clarified, but there is sufficient evidence to link the immune system interaction with the ENS in the syndrome's pathophysiology. Notably, inflammation in IBS is marked and considered a significant feature in diagnosis, including in patients with postinfectious IBS [60]. The immune mast cells in the submucosal plexus trigger multiple inflammatory responses and generate a neuroimmune response when interacting with enteric neurons. The signaling of mast cells to enteric neurons is via neurotransmitters and neurohormones such as histamine and tryptase, which exert an excitatory function on the submucosal plexus, and an increased density of such cells is correlated with visceral hypersensitivity [61]. Genes are also involved, some supporting neuronal functions associated with IBS [56].

6.2 Hirschsprung disease (HSCR)

HSCR is a primary enteric neuropathy and one of the most frequent gastrointestinal motility disorders, showing the absence of enteric ganglia mainly in the colon. The congenital absence of ganglia neurons at the submucosal and myenteric plexuses occurs following a failure in the migration process of cells from the enteric neural crest to the hindgut; thus, this disease is known as a neurochristopathy but also is known as congenital megacolon or intestinal aganglionosis [62, 63]. The absence of ganglia produces a reduced or no peristalsis at all, causing intestinal occlusion because of the cessation of the expelling of fecal material. HSCR has an incidence of 1/5000 newborns and is more prevalent in males, in a 4:1 ratio [62].

6.3 Achalasia

Achalasia is a rare disorder affecting the motility of the esophageal region, characterized by the loss of enteric neurons and inhibitory postganglionic neurons that produces the absence of peristalsis of the tubular esophagus and impaired relaxation of the lower esophageal sphincter, involved in the swallow reflex. Symptoms include dysphagia, heartburn, regurgitation, chest pain, and weight loss. There is no total clarity of the etiology, but evidence exists that it is associated with autoimmune processes to still unknown antigens [64]. Furthermore, similar manifestations are found in some cases, as those related to the Chagas disease [65, 66].

6.4 Chronic constipation

Constipation by itself is not a disease, but it is considered a widespread gastrointestinal disorder that turns out to be the primary symptom to diagnose a disease.

During constipation, defecation is difficult, accompanied by pain and stiffness (Forootan 2018), which is more frequent in women [67]. It is classified into two types, primary and secondary. Primary refers to dysregulation of neuromuscular activity within the colon and rectum, sometimes called functional constipation, that includes irritable bowel syndrome, and slow-transit constipation, caused by dysfunction of the smooth muscle activity in the colonic region. The secondary is nonspecific because constipation can respond to multiple factors such as metabolic problems, intake of medications, diet, neurological disorders, or colon diseases [68].

6.5 Autism spectrum disorder (ASD)

ASD is a neurodevelopmental disorder characterized by two domains, social and communicative difficulties, and restricted and repetitive behaviors, that appear early in childhood. In addition to the whole manifestations, ASD is commonly accompanied by many comorbid conditions that include a significant prevalence of gastrointestinal alterations such as chronic gastrointestinal dysfunction (diarrhea, constipation, reflux, etc.), or food intolerance [69, 70]. Also, ASD children show physiological alterations such as increased intestinal permeability, microbiota modifications, and intestinal infection [71]. Furthermore, the upper and lower gastrointestinal tract can show mild to moderate inflammation [72].

More than 90% of ASD children have feeding problems with detrimental effects; one of the causes is the modification of the microbiome, suggesting that ASD behaviors could benefit from interventions to restore microbial balance [73]. Such modification, known as gut dysbiosis, has been investigated by studying the bacterial genus *Clostridium*, which contributes essential species to the human microbiome [74]. Data suggest an association of ASD with an increase in *Clostridium* and a decrease in other microbiome species [75]. Notwithstanding, dysbiosis of other species is also correlated to autism [76]. Beyond the microbiome, several changes occur in enteric neurons and enteric glia [77] that affect the appropriate communication to central structures [78], making the microbiota–gut–brain axis a pivotal center to study the underlying basis of autism.

6.6 Alzheimer's disease (AD)

AD is a neurodegenerative condition showing a progressive deterioration of higher brain functions, mainly memory, and is considered one of the most common dementias [79]. The striking tissue features are the presence of extracellular accumulations of the amyloid beta (Aβ) peptide, or amyloid plaques, and neurofibrillary tangles [80]. Unfortunately, the evidence to explain the correlation between ENS and AD remains scarce. However, AD patients suffer from gastrointestinal alterations [81], that Aβ is also accumulated in enteric neurons producing a number reduction and suggesting that ENS dysfunction is ligated to AD [82] and that gut dysbiosis could also be correlated to AD [83].

6.7 Parkinson's disease (PD)

PD is a neurodegenerative disease with a progressive reduction in the number of dopaminergic neurons in the substantia nigra pars compacta (SN), associated with abnormal cytoplasmic deposits mainly of alpha-synuclein, known as Lewy bodies [84, 85]. It is usually diagnosed by the motor characteristics of the patient, such as

progressive tremors, jaw rigidity, and bradykinesia [86]. Data indicate that Lewy bodies are also found in enteric neurons, correlated with gastrointestinal motility and constipation [87].

6.8 Chagasic megacolon

Chagas disease is caused after an infection by *Trypanosoma cruzi*. It is an endemic disease in South America, Central America, and Mexico. The acute symptoms often go unrecognized, but patients can develop many physiological alterations, including motor dysfunction of the gastrointestinal tract [88]. The mechanism of enteric neuronal lesions in the intestinal plexuses generates aperistalsis and megasyndromes. In the case of megacolon, motility problems are associated with colon enlargement and constipation, showing the widening of the luminal region and muscle hypertrophy. Such lesions occur because the infection causes immune reactions that progressively become cytotoxic, producing oxidative stress and a reduction in the number of neurons [89].

7. Conclusions

The ENS is a sophisticated nervous system by itself, with an elaborated organization immersed in the whole gastrointestinal tract, responsible for regulating gut physiology. Its million neurons include intrinsic and extrinsic neural pathways with a significant function independent from the central nervous system. This attribute insinuates that the ENS should be considered as a second brain. To sustain all functions around food processing, the complex network of neurons and glial cells and the relationships with the microbiome organize an exceptional bidirectional communication with the CNS and an intrinsic communication with its own afferents, interneurons, and motor neurons. These pathways are essential for maintaining a healthy gut and general homeostasis. Dysregulation of such networks produces a wide range of diseases. Thus, research on the ENS and its interaction with the CNS must grow to give new insights into the function and pathophysiology of the gastrointestinal tract to develop new and better therapeutic approaches.

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Conflict of interest

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