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Version of Record: https://www.sciencedirect.com/science/article/pii/S0028390821002768
Manuscript_c86edbbedf9fa924bd5b76609a079243

Review **Neuropharmacology**

Interactions between the microbiota and enteric nervous system during gut-brain disorders

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ABSTRACT

For the last 20 years, researchers have focused their intention on the impact of gut microbiota in healthy and pathological conditions. This year (2021), more than 25,000 articles can be retrieved from PubMed with the keywords “gut microbiota and physiology”, showing the constant progress and impact of gut microbes in scientific life. As a result, numerous therapeutic perspectives have been proposed to modulate the gut microbiota composition and/or bioactive factors released from microbes to restore our body functions. Currently, the gut is considered a primary site for the development of pathologies that modify brain functions such as neurodegenerative (Parkinson’s, Alzheimer’s, etc.) and metabolic (type 2 diabetes, obesity, etc.) disorders. Deciphering the mode of interaction between microbiota and the brain is a real original option to prevent (and maybe treat in the future) the establishment of gut-brain pathologies. The objective of this review is to describe recent scientific elements that explore the communication between gut microbiota and the brain by focusing our interest on the enteric nervous system (ENS) as an intermediate partner. The ENS, which is known as the “second brain”, could be under the direct or indirect influence of the gut microbiota and its released factors (short-chain fatty acids, neurotransmitters, gaseous factors, etc.). Thus, in addition to their actions on tissue (adipose tissue, liver, brain, etc.), microbes can have an impact on local ENS activity. This potential modification of ENS function has global repercussions in the whole body *via* the gut-brain axis and represents a new therapeutic strategy.

Keywords: Gut microbiota/Enteric nervous system/Gut-brain axis/Enterosynes/Neurodegenerative disorders

1. Introduction

Since the early 2000s, the number of studies showing the important role of gut microbiota as a promising therapeutic target has grown substantially (Cani, 2018). Modulation of the gut microbiota by using probiotics (Paone and Cani, 2020; Wieers et al., 2019) or prebiotics (Roberfroid et al., 2010; Van Hul and Cani, 2019) has a real impact on intestinal physiology, including the gut barrier (Geurts et al., 2014; Paone and Cani, 2020; Regnier et al., 2021) and gut inflammation (Cani and Jordan, 2018), which play key roles in the development of numerous pathologies that are largely described in the literature. Therefore, identifying and controlling intestinal bacterial function represent an innovative approach to treat multiple pathologies associated with gut microbiota dysfunction, such as during cancer, metabolic disorders, visceral pain and neurodegenerative disorders.

The gut microbiota has a great capacity to interact with the host by releasing different bioactive molecules, such as bioactive lipids/peptides, gas, and neurotransmitters, that could modify host endocrine functions (Rastelli et al., 2019) and the nervous system. In this case, modification of gut microbiota composition and function can directly and indirectly modulate (*via* an impact of gut hormone release) the activity of the central nervous system (CNS) to control various physiological functions in the whole body (Cani and Knauf, 2016). Another indirect interaction between gut microbiota and the brain requires the enteric nervous system (ENS), which is directly linked to the CNS (Cani and Knauf, 2016). In fact, evidence shows that this partnership between the gut microbiota and neurons is now recognized as a crucial element for the postnatal development of the ENS and CNS (Margolis et al., 2021). Recently, we regrouped all molecules that could target the ENS to treat pathologies under the name enterosynes (Knauf et al., 2020). In fact, bioactive molecules released by specific gut microbes could also be considered enterosynes on the condition that their release has an effect on ENS activity. The purpose of this review is to describe the molecular interactions between the gut microbiota and ENS to modulate the gut-brain axis in normal and pathological conditions.

2. Overview of the enteric nervous system (ENS)

2.1 Structural organization of the ENS: A rapid focus

The ENS is composed of 400-600 million neurons in humans (Furness, 2012) distributed in thousands of small ganglia and spreads all along the gastrointestinal (GI) tract starting from the upper esophagus to the anal sphincter. The majority of the ENS originates from neural crest (NC) cells (Lake and Heuckeroth, 2013). Vagal and sacral-derived NC cells engage in different strategies to migrate

and colonize the intestine (Burns and Le Douarin, 2001). It becomes functional in the last third of gestation in humans and continues to develop even after birth (Hao et al., 2016; Rao and Gershon, 2018). Alterations in normal ENS development could lead to congenital disorders such as Hirschsprung disease, a disease occurring in 1 in 5000 births that is characterized by a functional obstruction of the GI tract caused by aganglionic colonic segments (Heuckeroth, 2018; Luzon-Toro et al., 2020). This is associated with different symptoms, such as constipation, vomiting, growth failure and abdominal distention (Kessmann, 2006). In fact, the general organization of the ENS is in place at birth, but "the functional maturation of intestinal networks is completed within the microenvironment of the postnatal gut under the influence of gut microbiota", as reviewed by Obata and Pachnis (Obata and Pachnis, 2016). In addition, this postnatal development of the ENS requires complex crosstalk between immune cells and microbial factors (Kabouridis and Pachnis, 2015).

The ENS is composed of enteric glial cells and enteric neurons (Furness, 2012) that contact different cells, including muscle, epithelial cells, interstitial cells of Cajal (ICCs), blood vessels and immune cells. Enteric glial cells outnumber neurons in the ENS and are essential for structural and nutritional support of enteric neurons as well as many other additional roles (neuromediator expression, neurotransmission and neuroprotection) (De Giorgio et al., 2012; Neunlist et al., 2014). Enteric glial cells are localized in all layers of the intestinal wall. In a recent review, Seguella and Gulbransen (Seguella and Gulbransen, 2021) described six main types of enteric glia. This classification is based upon the local subpopulations of glia defined in the gut based on their morphology, anatomical location and localization either within or outside of enteric ganglia.

On the other hand, ICCs are responsible for the generation of electrical impulses to smooth muscle cells and are often called "pacemaker cells", thus initiating peristaltic wave gut movement (Lee et al., 2007; Sanders et al., 2016; Takaki, 2003). Intestinal reflexes are controlled by the ENS, which is organized into two main plexuses. The submucosal plexus (also called Meissner's plexus) lies within the connective tissue of the submucosa of the intestinal wall, and the myenteric plexus (or Auerbach's plexus) lies between the longitudinal and circular muscle layers. Several differences exist in the ENS in terms of structure along the GI tract and have a major role in many physiological processes, including secretion, exchange of fluids across the mucosal epithelium, barrier function, local blood flow, immune system and gut motility (Furness et al., 2014). Enteric neurons are classified as afferent or efferent neurons, interneurons and motoneurons (Brierley and Linden, 2014). Intrinsic primary afferent neurons (IPANs) detect mechanical or chemical stimuli (food intake, mechanical distortion, etc.) to relay physiological information to the rest of the ENS neurons (Furness et al., 2004). Interneurons are another class of neurons defined as "ascending" when orally detected and "descending" when anally directed. They are located between the IPANs and motor/secretomotor

neurons and participate in interneuronal communication (Costa et al., 2000). Ascending interneurons were described as cholinergic, while 3 classes of descending interneurons were identified: 1) neurons that release acetylcholine, nitric oxide (NO) and vasoactive intestinal peptide (VIP); 2) neurons able to release acetylcholine and somatostatin; and 3) neurons that synthetize acetylcholine and serotonin (5-HT) (Furness, 2000).

Finally, excitatory and inhibitory motoneurons innervate smooth muscle cells and the muscularis mucosae of the GI tract. The major neurotransmitters released by excitatory neurons are acetylcholine and substance P (Drokhlyansky et al., 2020), while inhibitory neurotransmitters include NO and VIP (Furness et al., 2014). In fact, choline acetyl transferase (ChAT)-expressing neurons (which produce acetylcholine) and neuronal nitric oxide synthase (nNOS)-expressing neurons (that produce NO) represent a large population compared to all ENS neurons (Beck et al., 2009). Some neurons express both neurotransmitters (Beck et al., 2009; Murphy et al., 2007), and the ratio of ChAT/nNOS neurons differs between intestinal regions (Beck et al., 2009). These neurons are responsible for GI tract motility and propulsive contraction toward the anus. In the submucosal plexus, secretomotor/vasodilator neurons reach the mucosa and submucosa to regulate secretion and blood flow (Vanner and Macnaughton, 2004).

In addition to intrinsic enteric neurons, the gut is also innervated by extrinsic neurons that facilitate communication with the brain. In a very complete review, Brierley and Linden clearly described the different interactions/projections between the gut and extrinsic neurons (Brierley and Linden, 2014). The authors classified extrinsic neurons as extrinsic sensory afferent neurons (vagal and spinal afferences) and efferent sympathetic/parasympathetic neurons (that regulate gastrointestinal functions), which are all implicated in physiological processes described below. Gut-extrinsic neurons include somatosensory neurons (“gut-brain axis”) and autonomic neurons (“brain-gut axis”), leading to a “gut-brain-gut” regulatory loop. Neuroanatomical mappings show distinct localization of cell bodies for these different neurons, i.e., in peripheral sensory or autonomic ganglia (nodose ganglia and dorsal root ganglia) for afferent neurons that project to the spinal cord or to the brainstem, where cell bodies for efferent neurons are located (Brierley and Linden, 2014; Jacobson et al., 2021). Recently, Kaelberer *et al*. identified that some enteroendocrine cells called neuropods now have the great capacity to make direct synaptic contact with the vagus (Kaelberer et al., 2018). At the interface between an endocrine cell and a neuronal cell, neuropods are implicated in the detection of luminal nutrients such as glucose to inform the brain of the nutritional state. This mechanism requires glutamate release by the neuropods in the gut to rapidly transduce luminal stimuli to the central nervous system.

2.2 The "gut-brain" and "brain-gut" axis

2.2.1 Neuronal communication

Even if the ENS is capable of functioning independently from the CNS, i.e., regulating local motility and secretion, both are in continuous bidirectional crosstalk. The role of the "gut-brain" axis (GBA) is to monitor, integrate and inform the brain from variations in intestinal function, such as the enteric reflex, intestinal permeability, presence of nutrients, and endocrine signaling (Mayer, 2011). In the other direction, the "brain-gut" axis is also able to modulate enteric function to control gut motility and permeability, which has an impact on bacterial composition (Rhee et al., 2009).

In fact, afferent sensory neurons project into the brain, constantly monitoring the gut for physical, mechanical or chemical stimuli and informing the brain about the intestinal physiological status (Williams et al., 2016). The afferent gut-brain connection is classified as vagal and spinal routes. Briefly, vagal afferent sensory neurons are distributed all over the digestive wall (myenteric and submucosal ganglia, smooth muscle cells, blood vessels) and project in the brainstem mostly in the nucleus tractus solitarius (NTS) (Kupari et al., 2019; Travagli et al., 2006). Due to their function, vagal afferent neurons are able to detect stretch, molecules such as bacterial products, hormones and neurotransmitters (Raybould, 2010). Additionally, spinal afferents have cell bodies in dorsal root ganglia and project centrally to the spinal cord (Brierley and Linden, 2014). From a pathological point of view, the stimulation of spinal afferents is associated here with pain sensations, intestinal discomfort, bloating and urgency.

Like most of the organs in the whole body, the intestine is under the control of the autonomic nervous system since it receives parasympathetic efferences through the vagus nerve and sympathetic efferences through splanchnic nerves (Browning and Travagli, 2014). The sympathetic nervous routes are important in several inhibitory effects on GI muscle cells, mucosal secretion and blood flow. The parasympathetic nervous routes are both excitatory and inhibitory, allowing complex regulation of the GI tract. Vagal innervations that originate from the dorsal motor nucleus project their nerve endings in the stomach, small intestine and colon (Browning and Travagli, 2014). Efferent communication allows the brain to influence the activity of numerous effectors, such as epithelial cells, enteric neurons, smooth muscle cells, ICCs, and immune cells, to regulate key functions, including the release of gut factors (neurotransmitters, hormones, and immune factors) and GI motility (Browning and Travagli, 2014).

By using a plethora of innovative technologies (circuit-tracing methods, functional and chemogenetic experiments), Muller *et al*. (Muller et al., 2020b) demonstrated that alteration of gut microbiota is able to directly activate intestinal vagal afferent signals to control glutamatergic brainstem neurons.

Here, glutamatergic neurons have the capacity to drive sympathetic activity, which is known to control gastrointestinal transit. Therefore, this modulation of the gut-brain axis by microbiota has an impact on efferent sympathetic nerves that regulate gut motility *via* the sympathetic celiac-superior mesenteric ganglion. This "direct" regulation of extrinsic neurons from the autonomous nervous system by microbial actors could represent a key regulatory point in understanding the establishment of numerous pathologies and lead to the proposal of novel therapies.

2.2.2 Hormonal communication

In addition to nervous communication, the GBA uses other routes of communication to monitor stimuli/signals coming from the GI tract, such as the hormonal pathway. In fact, enteroendocrine cells (EECs) are intestinal cells specialized in the release of hormones. EECs scatter through the epithelium of the digestive tract. Depending on the gut region, the repartition of EECs can differ, suggesting different roles of these cells throughout the digestive tract. In an elegant review, Gribble and Reimann (Gribble and Reimann, 2019) revealed that EECs can respond to various stimuli from the proximal part to the distal part of the gut. For example, EECs from the proximal gut (the first site of nutrient entry in the intestine) have the possibility of responding directly to nutrients, and EECs from the distal gut, which are in close proximity to the gut microbiota, are known to release hormones in response to microbial factors. Gut hormones released in the portal vein may act in different parts of the body (pancreas, liver, gut, etc.) (Regnier et al., 2021), and one can suppose that a gut hormone produced in a specific part of the intestine could exert its physiological effect at the exact opposite site of its intestinal site of production. In addition, from a molecular point of view, EECs present a high diversity in their capacity to synthetize and release various hormones (Depoortere, 2014). Taking into account the diversity of EEC types (localization, type of hormone secreted) and receptor localization (extrinsic or intrinsic neurons in the gut) is an important point in deciphering the gut-brain message (Berthoud et al., 2021). Many gut hormones exist, and we have chosen only some examples to describe this interaction between the gut and the brain.

Enteroendocrine L cells secrete glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) (Cani and Knauf, 2016). Receptors for these peptides are notably expressed in the ENS, vagal afferents and CNS (De Silva and Bloom, 2012; Richards et al., 2014). Related to their numerous physiological functions, one of the well-known effects of both peptides is their implication in the control of food intake. As described above, vagal afferent terminals located in the GI tract are in close proximity to the epithelium. Indeed, some hormones secreted by EECs act *via* a paracrine mode of action on these vagal afferent fibers to inform the brain. This "gut-brain" neuronal stimulation controls various

functions, including food intake (Sam et al., 2012) and glucose metabolism (Knauf et al., 2020). In detail, PYY is mainly secreted in the ileum and colon after nutrient intake that includes lipids, carbohydrates and proteins (Covasa et al., 2019). Two forms of PYY exist: its full form PYY_{1-36} and a truncated form PYY_{3-36} , which is the circulatory form (Persaud and Bewick, 2014). PYY_{3-36} in rodents may transmit satiety signals, thus reducing food intake at least *via* vagal afferents and the arcuate nucleus (Batterham et al., 2002; Koda et al., 2005).

GLP-1 is an incretin hormone released by enteroendocrine L cells, especially in the distal jejunum, ileum and colon, in response to luminal nutrients (Burcelin et al., 2007). It has a key role in stimulating insulin release by the pancreas and inhibiting glucagon secretion, increasing insulin sensitivity, and reducing gastric emptying and blood flow (Burcelin et al., 2007). In fact, GLP-1 receptors are distributed in pancreatic β cells, enteric neurons, the vagus nerve and the hypothalamus (Cork et al., 2015; Pyke et al., 2014; Richards et al., 2014). Experiments have shown that peripheral or central GLP-1 administration results in a drastic decrease in food intake in rodents (Muscogiuri et al., 2017; Turton et al., 1996), and the peripheral satiety action of GLP-1 is abolished following bilateral vagotomy, highlighting the importance of the "vagal-brainstem-hypothalamic pathway" in this regulation (Abbott et al., 2005). Vagal afferents in the gut implicated in the control of food intake express GLP-1 receptors (Al Helaili et al., 2020). Chronic high-fat diet treatment in mice leads to the desensitization of vagal afferents to GLP-1, which provokes the impairment of satiety signals from the gut (Al Helaili et al., 2020). Notably, GLP-1 receptors are expressed in enteric neurons, particularly in nNOS neurons in the duodenum and in the colon, suggesting a direct relationship between these two actors (Amato et al., 2010). Indeed, intraperitoneal injection of the GLP-1 agonist exenatide increases Fos-like immunoreactivity in the myenteric and submucosal neurons of the duodenum (Washington et al., 2010). In addition, GLP-1 is able to stimulate myenteric NO release (Amato et al., 2010; Rotondo et al., 2011), a major neurotransmitter known to inhibit the contraction of intestinal smooth muscle cells (Knauf et al., 2020). Activation of myenteric NO release by GLP-1 in enteric neurons could explain the inhibitory action of GLP-1 on postprandial gut motility (Halim et al., 2018).

Cholecystokinin (CCK) is a gut peptide mainly secreted by enteroendocrine L cells in the upper small intestine (i.e., duodenum and jejunum). Once again, the GBA involves the close proximity of EECs in the mucosal epithelium to the vagal afferents (Powley et al., 2011). Exogenous administration of CCK results in reduced food intake, inhibition of gastric emptying and stimulation of pancreatic exocrine secretion in a vagal efferent nerve activation-dependent manner (Raybould, 2007). Moreover, when CCK1 receptor (CCK1R, a CCK receptor expressed in vagal afferent terminals) is disrupted in mice, activation of vagal afferents is reduced in response to intestinal lipids (Whited et al., 2006). All this

information suggests that CCK produced in response to food intake could activate the vagus nerve *via* CCK1R in vagal afferents and transmit the information to the brain, thus regulating satiety and other physiological parameters.

Finally, enterochromaffin cells are an enteroendocrine cell subtype that produces the majority of serotonin (5-HT) in the body and are implicated in many physiological processes, including GI motility, secretion, nausea and pain perception (Gershon and Tack, 2007). Studying 5-HT and gut-brain communication has proven to be challenging in recent years. Notably, Bellono *et al.* exploited cultured intestinal organoids combined with single-cell technology to conclude that enterochromaffin cells are able to excite neural afferent fibers *via* synaptic connections (Bellono et al., 2017). In fact, this is an example of a signaling system between the intestinal epithelium and the GBA allowing monitoring of GI changes in the luminal environment.

3. Interaction between gut microbiota and ENS

3.1 Microbiota-releasing factors

The human microbiota consists of the entirety of the microorganisms inhabiting the human body. It is estimated that the total number of bacteria in a 70 kg "reference man" is $3.8x10^{13}$, where most of the microbes reside in the intestine and are called "gut microbiota" (Sender et al., 2016). The human GI tract is colonized by multiple microorganisms, including bacteria, archaea, fungi, viruses and phages (Sender et al., 2016). Gut colonization by microbiota occurs immediately after birth during a 3-year perinatal critical window development in which the gut microbiota undergoes a series of ecological modifications (Ratsika et al., 2021). After that, the adult-like composition of gut microbiota remains for the rest of our life as an invisible partner influencing our health and many other parameters. The gut microbiota is not homogeneous throughout the GI tract, as it has been described that the duodenum harbors approximately 10^3 bacteria/g, whereas 10^{12} bacteria/g are found in the colon (Sekirov et al., 2010). At the taxonomic level, the gut microbiota composition is dominated by bacteria belonging to the Firmicutes and Bacteroidetes phyla (Eckburg et al., 2005), but its composition and activity can vary throughout time and based on multiple factors during life. First, host-related factors such as age, sex, genetic background and the immune system impact gut microbiota composition (Jasarevic et al., 2016; Odamaki et al., 2016; Org et al., 2015). Second, external factors such as the diet or the use of antibiotics, specific drugs such as antidiabetic agents, proton pump inhibitors or other pharmacological agents might also have an influence on gut microbiota (Becattini et al., 2016; Vich Vila et al., 2020; Zhang et al., 2015). Third, numerous studies have highlighted that as mentioned above, diet is an important factor influencing gut microbiota

composition and activity, and it is far stronger than the effects of genetic background (Asnicar et al., 2021; Cani and Van Hul, 2021; David et al., 2014; Wu et al., 2011).

Thus, the gut microbiota is now considered a potential therapeutic target for numerous pathologies (Cani, 2018) by bioactive factors (described below) that act *via* endocrine and neuronal routes (Gulla et al., 1989; Regnier et al., 2021).

3.1.1. Short-chain fatty acids (SCFAs)

SCFAs are the result of the microbial fermentation of nondigestible carbohydrates within the gut, producing mainly acetate, butyrate and propionate. In turn, these bacterial SCFAs can be used by the host. For example, acetate of bacterial origin is a precursor for the hepatic synthesis of long-chain fatty acids and glycerophospholipids (Kindt et al., 2018). Bacterial butyrate is described as a primary source of energy for colonocytes (Donohoe et al., 2011), and butyrate and propionate have a gluconeogenic role in the liver and gut (De Vadder et al., 2014). SCFAs are also able to bind and activate the specific G-protein coupled receptors GPR-43 (also referred to as FFAR2) and GPR-41 (referred to as FFAR3) (Brown et al., 2003; Kim et al., 2013). Several studies have described the expression of these receptors in many tissues and cell types, including enterocytes, enteroendocrine cells and immune cells (Le Poul et al., 2003; Tazoe et al., 2009). SCFAs are legitimately considered key messengers of the communication between gut microbiota and the host, modulating interactions impacting host physiology, particularly the GBA (De Vadder et al., 2014).

3.1.2. Neurotransmitters and gaseous factors

The microbiota is also able to produce molecules that belong to the neurotransmitter family that could have a “local” physiologic action or a “central” action *via* the GBA. Clarke *et al*. reviewed neurotransmitter-producing bacterial strains, including those that produce serotonin, dopamine, noradrenalin, GABA, acetylcholine and histamine (Clarke et al., 2014).

The impact of monoamines (and not only monoamines from bacterial origins) in the ENS is well described by Neuhuber and Wörl (Neuhuber and Worl, 2018). To propose one example, and apart from its production by enzymatic reaction, histamine is also produced by microbial decarboxylation of amino acids (Durak-Dados et al., 2020). Interestingly, the gut microbiota is capable of producing histamine under physiological conditions, where it might participate in gut immunity. Experiments have shown that histamine can exert anti-inflammatory effects by modulating interleukin-18

production in the gut (Levy et al., 2015). In addition to this well-known role in immunology, histamine can also directly modulate the activity of the ENS (Neuhuber and Worl, 2018).

Gut microbes can also influence tryptophan metabolism. In a recent review, Roth *et al*. (Roth et al., 2021) described how gut microbiota influences tryptophan metabolism directly and indirectly, leading to extraintestinal impacts such as behavior, depression and cognition. Among all tryptophan metabolic pathways, serotonin is largely studied in the literature, with a clear link between the gut and the brain in normal and pathological states (see Point 4.4). *Clostridium sporogenes* is able to decarboxylate tryptophan from the diet to tryptamine (Williams et al., 2014), a neurotransmitter known to deplete the myenteric plexus of endogenous serotonin (Takaki et al., 1985). In turn, serotonin released by tryptamine acts on myenteric cholinergic neurons to stimulate smooth muscle contraction (Takaki et al., 1988).

Another neurotransmitter synthetized by the gut microbiota is γ-aminobutyric acid (GABA) as a result of the decarboxylation of L-glutamate. GABA is produced by members of the *Lactobacillus* and *Bifidobacterium* genera and is involved in many features in the gut, including intestinal motility, gastric emptying, and visceral pain (Hyland and Cryan, 2010).

Additionally, gut microbes are able to produce and release various types of gases, such as NO, methane, hydrogen and carbon monoxide (Pimentel et al., 2013; Vermeiren et al., 2009). Bacteria synthetize NO from the reduction of nitrite (Tiso and Schechter, 2015) and from nitric oxide synthase (Crane et al., 2010). Consequently, these gases can cross the epithelium and modify gut function, including the ENS (Cani and Knauf, 2016). A recent review from Kalantar-Zadeh *et al*. described the potential pathogenic/physiological/therapeutic actions of these bacterial gaseous factors (Kalantar-Zadeh et al., 2019).

3.2 Interactions with the ENS

The interaction between the gut microbiota and the ENS could be direct or indirect. It is now well established that gut microbes (and their released factors) could communicate with the CNS but also with the ENS through direct and indirect action on neurons. Direct actions could require Toll-like receptors (TLRs). In fact, TLR3, 4 and 7 are expressed in both the myenteric and submucosal plexi of the intestine (Barajon et al., 2009), suggesting that the ENS might be directly activated by bacterial lipopolysaccharides (LPS) from gram-negative bacteria to modulate processes such as GI motility and secretion and inform the brain about the gut physiological status. In addition, TLR2 and TLR9 are capable of modulating the ENS inflammatory response to microbial LPS (Brun et al., 2013; Burgueno

et al., 2016). Functionally, mice deficient in TLR4 display decreased transit *in vivo* and changes in neural numbers in colonic and ileal enteric neurons (Anitha et al., 2012). In addition, TLRs are also expressed in glial cells (Barajon et al., 2009). Moreover, microbiota has been suggested to be required for enteric glial migration and for the postnatal development of enteric glial cells in the intestine. Experiments using germ-free mice resulted in a significantly reduced number of glial cells, and restoring conventional microbiota rescued this deficiency (Kabouridis et al., 2015). It is well established that TLRs are expressed on immune cells in the gut. The gut microbiota generates factors that are recognized by TLRs of the immune system, leading to the release of proinflammatory cytokines (Semin et al., 2021). This phenomenon notably has an impact on the intestinal epithelial barrier (Semin et al., 2021) and gut-brain axis (Caputi and Giron, 2018), thus participating in the establishment of pathological states (see Point 4).

Another mode of "direct" communication requires IPANs. IPANs are ideally localized to integrate information coming from gut bacteria because their axons extend into the gut mucosa. Of interest, IPANs isolated from germ-free mice were reported to be electrophysiologically different from IPANs isolated from normal mice, reflecting decreased excitability – a process that can be restored when germ-free mice are colonized with conventional microbiota (McVey Neufeld et al., 2013).

Regarding "indirect" interactions, enteroendocrine L cells produce peptides, including GLP-1 and PYY, as previously mentioned. Studies have shown that when the microbial composition changes with the use of prebiotics, GLP-1 and PYY levels are altered (Cani et al., 2004; Delzenne et al., 2005). Of note, prebiotics also increase SCFA abundance, and evidence suggests that binding to its receptors (GPR-41 and GPR-43) promotes the release of GLP-1 and PYY (Psichas et al., 2015; Tolhurst et al., 2012). Immunohistochemistry experiments show that GLP-1 receptors are expressed on enteric neurons (Amato et al., 2010). Activation of these receptors stimulates the release of enteric NO, resulting in gastric antrum relaxation (Rotondo et al., 2011) and inhibition of postprandial motility in humans (Halim et al., 2018). Compiling the literature showing the close relationship between SCFAs and GLP-1 (Everard and Cani, 2014), we can speculate that the ENS is also an indirect target for gut microbiota to control the GBA and its associated functions, such as food intake (Washington et al., 2010).

4. **Gut-brain disorders associated with gut microbiota-ENS dysfunction**

Several studies have associated enteric neuropathy, dysbiosis and gastrointestinal symptoms with neuronal disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), autism spectrum

disorder (ASD), type 2 diabetes (T2D) and others (Cryan et al., 2020). These pathologies have a clear common point corresponding to the alteration of the GBA associated with gut microbiota dysfunction. All these pathologies share a very similar process associated with alterations in the gut microbiota population and/or factors released by the gut microbiota that have an impact on host cellular targets such as enteric neurons, immune cells or enteroendocrine cells (Cani and Knauf, 2016). Then, modification of the gut microbiome could be used to "combat neurodegeneration" to cite the author (Sasmita, 2019). As the ENS is 1) in close proximity to the gut microbiota and 2) one of the major actors implicated in the interaction between the gut and the brain, we will discuss here the role of gut microbiota-ENS crosstalk in the establishment of pathological states.

4.1 Parkinson's disease

PD is a neurodegenerative disorder characterized by the intraneuronal accumulation of misfolded α-synuclein into inclusions named Lewy bodies and progressive loss of dopaminergic neurons in the *substantia nigra*. This process leads to clinical symptoms, including tremor at rest, rigidity and bradykinesia, as well as nonmotor symptoms, such as depression, anxiety and loss of smell (Berg et al., 2015; Mahul-Mellier et al., 2020). PD is believed to be a sporadic disorder in which environmental factors and age are the main risk factors, but approximately 15% of patients have a familial history of PD (Papapetropoulos et al., 2007). Unfortunately, current medical treatments remain symptomatic, but new therapeutic strategies are constantly emerging (Hayes, 2019; Zhang et al., 2021a).

It is now clear that PD involves more than just central motor impairment. Gastrointestinal dysfunctions such as constipation, dysphasia or delayed gastric emptying (Khoo et al., 2013) are suggested as early manifestations of the disease (Chaudhuri and Schapira, 2009). GI dysfunctions occur in up to 30% of PD patients in the premotor stage of disease evolution, preceding CNS involvement and motor symptom development, and are only exacerbated in advanced Parkinsonism. In the early 2000s, Braak and colleagues suggested that the sporadic form of PD may originate from the gut, as they observed that aggregated α-synuclein was present in the stomach and gut of PD patients. They hypothesized a stage progression of the disease where misfolded α-synuclein occurs in the ENS and then spreads in a prion-like manner through the gut-brain axis *via* the vagal nerve and the dorsal motor nucleus of the vagus (DMV) to the CNS (Braak et al., 2006; Braak et al., 2003). Evidence supporting this theory emerged with experiments on rodent models, as well as other models. Just before the brain, the first Lewy bodies were detected in the intestine of premotor PD patients (Harsanyiova et al., 2020), in the olfactory bulb and in the lower brainstem associated with

olfactory disturbances, rapid-eye-movement sleep behavior disorder and autonomic dysfunction (Meissner, 2012). This “body-first” theory of PD (“body” is for the enteric or peripheral autonomous systems) is real and well described, but the establishment of the pathology seems to be more complicated. Indeed, Horsager *et al*. (Horsager et al., 2020) suggest the existence of “brain-first” and “body-first” subtypes of Parkinson’s disease.

In rodents, α-synuclein injected into the intestinal wall of rats or into the duodenal and pyloric muscular layers of mice can be transported *via* the vagal nerve to the brain (Holmqvist et al., 2014; Kim et al., 2019). In patients who underwent full truncal vagotomy, the risk of PD was decreased, strongly supporting the role of the vagus nerve in PD progression (Svensson et al., 2015). However, whether this theory might represent a universal model of PD progression is still under debate, as other routes for PD progression are suggested in the literature (Kalaitzakis et al., 2008). Moreover, α-synuclein is believed to be transported both in retrograde and anterograde movements *via* the vagus nerve, as α-synuclein injected into the rat midbrain was shown to reach and accumulate in the gastric wall (Ulusoy et al., 2017).

An increasing number of studies are describing a difference in gut microbiota composition in patients with PD compared to healthy patients, and scientific interest has grown quickly to decipher the mechanisms involved. For instance, the prevalence of *Helicobacter pylori* (HP) infection is found to be higher in PD. Different hypotheses explaining HP involvement in PD have been suggested (Camci and Oguz, 2016). First, HP infection affects the bioavailability of L-Dopa (a precursor of dopamine used as a treatment for PD commercially known as levodopa) by altering the duodenal mucosae where L-Dopa is absorbed (Pierantozzi et al., 2001). Moreover, eradication of HP infection improves L-Dopa action (Hashim et al., 2014). Other possible mechanisms have been hypothesized. For example, HP-mediated glycosylation might generate cholesterol glucosides able to cross the blood-brain barrier to cause dopaminergic neuron degeneration (McGee et al., 2018) by stimulating the production of reactive oxygen species by the mitochondria (Panov et al., 2010). Finally, HP can induce an exaggerated neuroinflammatory response and apoptosis, both of which lead to neurodegeneration (Dardiotis et al., 2018).

In addition, numerous reports have described the association of this disease with gut microbiota dysbiosis. In particular, PD patients have a significant reduction in *Prevotellaceae* abundance in fecal samples (Scheperjans et al., 2015), while *Enterobacteriaceae* are found to be more abundant (Unger et al., 2016). In 2016, Sampson *et al*. showed a functional link between gut microbiota and PD disease using fecal transplantation from PD patients to germ-free mice. Their experiments suggested that gut microbiota is required for motor deficits in animal models and α-synuclein-related

pathologies, including PD (Sampson et al., 2016). It has also been reported that small intestinal bacterial overgrowth (SIBO), a disease defined by an abnormal excessive presence of microbes in the small intestine, might be associated with PD (Sampson et al., 2016). Finally, the altered gut microbiota is associated with a reduction in fecal SCFAs in PD (Unger et al., 2016). The reduction in SCFAs may induce alterations in the crosstalk between gut microbiota and ENS and thus contribute to gut dysmotility observed in patients. Recently, Hou *et al*. discovered that oral treatment with osteocalcin (an osteoblast-secreted protein) in rodents can modulate gut microbiota-derived propionate release. By acting on FFAR3, which is expressed in the enteric nervous system, propionate has a protective effect against dopaminergic neuron degeneration (Hou et al., 2021). Here, the authors discovered that ablation of enteric neurons blocked the prevention of dopaminergic neuronal loss by propionate in PD mice (Hou et al., 2021). In contrast, a recent review referred to the deleterious role of the bacterial endotoxin LPS in the establishment of PD (Bhattacharyya and Bhunia, 2021). In fact, as LPS is known to target ENS neurons and to affect α-synuclein aggregation (Bhattacharyya and Bhunia, 2021), it is now clear that gut microbiota is essential not only in promoting α-synuclein pathology and neuroinflammation (Sampson et al., 2016) but also in increasing intestinal permeability observed in PD (Forsyth et al., 2011). To conclude, numerous bacterial molecules and metabolites have immunomodulatory properties. Recently, Borie *et al.* clearly noted in an elegant review that intestinal inflammation induced by gut dysbiosis can lead to central neurodegeneration (Boeri et al., 2021).

4.2 Alzheimer's disease

AD is a multifactorial, age-related, and progressive neurodegenerative disease characterized by progressive memory loss and cognitive function that dramatically affects behavior and disrupts daily life (Alzheimer's, 2016). The prevalence of the disease increases with age, as 15% of Alzheimer's disease patients are 65 to 74 years old, while 44% are 75 to 84 years old. Sporadic Alzheimer's disease is the most common type (90%), although evidence suggests the existence of a heritable form of AD (Dorszewska et al., 2016). This disease is pathologically defined as aberrant extracellular accumulation of amyloid beta (Aβ) in senile plaques and intracellular accumulation of the hyperphosphorylated form of tau into neurofibrillary tangles (Crews and Masliah, 2010).

Growing evidence links dysbiosis and disturbance of the GBA to AD. Harach *et al.* highlighted the fact that microbiota is closely linked to the development of amyloid beta-related pathologies in rodents (Harach et al., 2017). Using Aβ precursor protein (APP) transgenic mice developing AD pathology similar to the human brain of AD patients (LaFerla and Green, 2012), they reported an increase in

Bacteroidetes and a reduction in Firmicutes in gut microbiota compared to wild-type mice (Harach et al., 2017). Moreover, colonization of germ-free APP mice with microbiota from wild-type mice showed less effective Aβ cerebral accumulation. Recently, experiments using a newly developed transgenic mouse model of AD known as ADLP^{APT} confirmed that transplantation of the fecal microbiota of healthy wild-type mice alleviates Aβ deposition and tau pathology (Kim et al., 2020). In humans, the fecal bacterial composition is also different between AD and healthy patients. The diversity of the gut microbiome in AD-diagnosed patients is lower, and its composition is different between age-/sex-matched individuals (Vogt et al., 2017). Specifically, the phylum Bacteroidetes was increased in the microbiome of AD participants, whereas the phylum Firmicutes and some genera, such as *Bifidobacterium*, were decreased. Finally, experimental evidence indicates that differences in the levels of LPS and SCFAs (Zhang et al., 2017) are associated with brain amyloid deposition. These results suggest that SCFAs and LPS represent a pathological link between gut microbiota and AD pathology (Marizzoni et al., 2020). Here, positive correlations exist among brain amyloidosis, plasma acetate, and LPS, and a negative correlation is observed between brain amyloidosis and butyrate. This suggests that the type of bacteria and the bioactive factors released could have beneficial or deleterious impacts on the GBA. Currently, the direct interaction of gut microbiota and ENS is not clearly described in the literature, but the link is relatively evident. Morphological analyses of AD-transgenic mice show modification of enteric neuron and glial cell plasticity, including a reduced density of the 3D network and reduced percentage of neuronal tissue per smooth muscle area (Van Ginneken et al., 2011), and this modification of ENS function correlates with the progression of the pathology (Semar et al., 2013). To reinforce this hypothesis, a recent study demonstrated the presence of amyloid beta peptide in the colon of AD-transgenic mice associated with gut motility disorder (Manocha et al., 2019). Future experiments must focus on the role of bioactive molecules released by gut microbiota and their impact on the ENS.

4.3 Autism spectrum disorder

ASD is a neurodevelopmental disorder diagnosed early in childhood. The diagnosis is based on behavioral symptoms such as social communication deficits, impaired communication and repetitive behavior (Lord et al., 2018). The genetic implication in ASD has proven to be very complex and heterogeneous, as it is also difficult to associate ASD with a particular molecular biomarker (De Rubeis and Buxbaum, 2015; Voineagu and Yoo, 2013). ASD is related to GI problems such as abdominal pain, diarrhea and constipation (Chaidez et al., 2014). A correlation exists between the presence of GI symptoms and ASD severity, where children with more severe autism experience

more severe GI symptoms and vice versa (Adams et al., 2011). Abnormal intestinal permeability is also disturbed, as it is higher in ASD patients than in control patients (de Magistris et al., 2010).

Recently, interaction within the GBA in the case of ASD has received considerable attention. Many studies have reported dysbiosis of the gut microbiota in ASD individuals. In particular, ASD patients present a lower abundance of *Akkermansia*, *Bacteroides*, *Bifidobacterium*, *E. coli* and *Enterococcus* but a higher abundance of *Faecalibacterium* and *Lactobacillus* (Finegold et al., 2010; Xu et al., 2019). Modifying the gut microbiota is a potential route to improve GI symptoms in ASD. The transfer of fecal microbiota from healthy donors to ASD children restores the dysbiotic gut microbiome to a healthy gut microbiome, thus improving symptoms for at least 2 years after microbial transfer (Kang et al., 2019; Kang et al., 2017). Similar to those observed in other neurological diseases described below, ASD patients present alterations in SCFA levels secreted by bacteria with positive or negative physiological impacts (Marrone and Coccurello, 2019). Mouse models of transgenic ASD show alterations in gut motility, fecal microbial communities and ENS neuron numbers (Hosie et al., 2019; Lee et al., 2020). Dell Colle *et al*. recently proposed that serotonin could be one molecule at the interface between the gut microbiota-ENS-GBA axis in ASD (Del Colle et al., 2020). Here, modulation of the gut serotonin signaling pathway by the gut microbiota could be a future therapeutic option for ASD patients.

4.4 Major depressive disorder

Major depressive disorder (MDD) is characterized by changes in brain functions such as unbalanced neurotransmitters, neuroplasticity decline and impaired neurogenesis (Chaudhury et al., 2015). There are multiple brain regions targeted by pathology, such as the ventral tegmental area or the nucleus accumbens, but evidence suggests an interdependence between all brain structures and various molecular actors involved in the pathogenesis of MDD (Filatova et al., 2021).

Additionally, depressed patients show gut-brain disturbances such as gastrointestinal disorders (Agrawal et al., 2020), changes in appetite (Simmons et al., 2016), and altered gut microbiota (Naseribafrouei et al., 2014). The gut microbiota of depressed patients is different from that of healthy patients since both microbiota diversity and richness are impacted by this disease (Jiang et al., 2015). Increases in Bacteroidetes and Proteobacteria together with a decrease in Firmicutes have been described (Jiang et al., 2015; Liu et al., 2016), and the use of a rodent model showed that fecal transplantation from depressed patients to germ-free mice resulted in more depressive symptoms in recipient mice (Zheng et al., 2016). Recent evidence shows that adherence to a healthy diet protects against depressive symptoms by modulating gut microbiota composition and the gut-brain axis

(Flowers and Ellingrod, 2015; Lang et al., 2015; Martins et al., 2021). Identifying the bacteria and/or their metabolites that restore this axis also remains to be determined since studies on the gut microbiota in MDD are inconsistent, as explained by Zhang *et al*. (Zhang et al., 2021b). In this recent study, the authors identified potential microbiota targets associated with the severity of depression, but the link between microbiota-ENS-MDD remains to be discovered.

Chronic depression is associated with a global alteration of the nervous system that includes the parasympathetic/sympathetic system, neuroendocrine axis and ENS (Agrawal et al., 2020). Among all potential targeted factors, the serotonin pathway could be a good candidate since serotonin neurons and receptors are expressed in the ENS. In a recent interesting review, Agrawal *et al*. assessed the link between the serotonin pathway in the gut and depression (Agrawal et al., 2020). The mechanism of action is not well described, but it was established that an oral selective serotonin reuptake inhibitor activates vagus nerve-dependent gut-brain signaling, resulting in a significant reduction in anxiety and depressive-like behaviors (McVey Neufeld et al., 2019). In addition, utilization of antibiotics in mice has an impact on motility, 5-HT and tryptophan hydroxylase-1 (the limiting enzyme for the synthesis of 5-HT by enterochromaffin cells (ECs)) levels in the colon (Ge et al., 2017). Thus, given that gut microbiota influences serotonin levels by acting on ECs (Yano et al., 2015), modulation of microbiota-EC interactions could be another alternative to treat MDD (Margolis et al., 2021).

4.5 Anxiety and stress

Anxiety is an emotional state in which stress exposure, whether from different sources (psychological, environmental or biological), triggers an anxiety response involving the hypothalamic-pituitary adrenal axis (HPA) and the immune system (Farzi et al., 2018). First, the microbiota is involved in the development and function of the HPA, which coordinates the response to stress within the body (Sudo et al., 2004). The HPA is dysregulated in the case of anxiety and depressive disorders because of cortisol levels and inflammation-related mechanisms (Keller et al., 2017). Modulating the intestinal microbiota using a probiotic (*Lactobacillus rhamnosus* JB-1) can have an effect on the vagus afferent nerve and then reduce stress- and anxiety-related behavior *via* a central GABA pathway (Bravo et al., 2011). Of course, the interaction between stress and microbiota is bidirectional, as chronic stress is responsible for gut microbiota diversity and composition alteration (Bailey and Coe, 1999). Additionally, the fecal microbiota of patients suffering from generalized anxiety disorder is different from that of healthy patients. Specifically, a lower abundance of

Faecalibacterium, *Eubacterium rectale*, *Lachnospira*, *Butyricicoccus* and *Sutterella* is found in patients with anxiety disorders (Jiang et al., 2018). Finally, several studies have described that germ-free mice exhibit increased motor activity and reduced anxiety compared to specific pathogen-free mice (Diaz Heijtz et al., 2011; Neufeld et al., 2011). Even if complementary studies are still needed to unveil every aspect of how the gut influences anxiety mechanisms, information collected thus far will help the scientific community to more deeply investigate the relationship between these two actors. Gut peptides present in enteric neurons and released in response to the influence of gut microbiota could be a solution to improve the function of the GBA (Lach et al., 2018).

4.6 Schizophrenia

Schizophrenia is a severe psychiatric disorder characterized by psychotic symptoms, cognitive impairment, and impaired motivation and social behavior (Owen et al., 2016). Previous studies have reported that schizophrenia is associated with numerous gastrointestinal comorbidities, such as inflammatory bowel syndrome (Gupta et al., 1997) and inflammatory bowel disease (Filipovic and Filipovic, 2014). Different studies have characterized a role for the GI tract immune system in the pathology of schizophrenia, with many inflammatory disturbances, and researchers propose that treatments to ameliorate brain symptoms of schizophrenia have to be supplemented with therapies to correct GI problems (Patterson, 2009; Severance et al., 2015). Various studies have reported differences in the gut microbial composition associated with schizophrenia (Nguyen et al., 2019; Schwarz et al., 2018; Shen et al., 2018). For example, in 2018, a study comparing 41 schizophrenic patients to a control group showed a significantly lower number of *Bifidobacterium*, *E. coli*, and *Lactobacillus* in feces but a higher content of *Clostridium coccoides* (Yuan et al., 2018). Another study revealed that *Lactobacillus* is elevated in patients reporting psychotic events compared to healthy patients (Schwarz et al., 2018). Again, we are only at the beginning of the comprehension of the microbiota-ENS-GBA crosstalk in this pathology, particularly during the pre- and postnatal development of the ENS/CNS (Cryan et al., 2019; Heiss and Olofsson, 2019).

4.7. Diabetes

Diabetes has a neurodegenerative impact on enteric neurons (Bagyanszki and Bodi, 2012; Knauf et al., 2020) that participate in peripheral diabetic neuropathy (Fujita et al., 2021; Jensen et al., 2021). In fact, T2D is associated with gastrointestinal symptoms such as abdominal pain, nausea, constipation and delayed gastric emptying, among other symptoms associated with dysbiosis and

enteric neuropathy. Identifying the role of the ENS in the establishment of these symptoms represents a real scientific interest (Knauf et al., 2020). Thus, studies linking gut microbiota-ENS-GBA are more described in the literature compared to other neurodegenerative disorders.

T2D is associated with enteric neuropathy, which includes modification of neuronal size, loss of myenteric duodenal neurons and degenerative changes such as axon swelling (Stenkamp-Strahm et al., 2013). In fact, numerous studies have described neuronal loss in diabetes. Indeed, injection of streptozotocin (STZ) in rats and observation of the whole mount proximal colon have shown a decrease in neuronal density and cell body size in myenteric neurons (Furlan et al., 2002). This neuronal loss is not restricted to the colon in diabetic rodent models, as similar results were found in the stomach (Fregonesi et al., 2001), ileum (Alves et al., 2006) and cecum (Zanoni et al., 1997). In humans, immunohistochemical staining of colon biopsies using specific neuronal markers has shown a reduced ganglion size, suggesting neuronal loss in diabetic subjects (Chandrasekharan et al., 2011). Enteric nitrergic neurons appear to be the most susceptible to diabetes-induced neuropathy (Bagyanszki and Bodi, 2012; Stenkamp-Strahm et al., 2013), as a reduced nNOS subtype of neurons is found in the stomach (Takahashi et al., 1997), duodenum (Stenkamp-Strahm et al., 2013), jejunum (Zandecki et al., 2008) and colon (Chandrasekharan et al., 2011) of diabetic models. This phenomenon has been reported in early stages of the disease. In mice, an eight weeks of high-fat diet feeding led to a reduced number of myenteric neurons, especially nNOS and VIP neurons, in the duodenum (Stenkamp-Strahm et al., 2013). A two-phase model explaining nitrergic neuron degeneration was suggested, with the first phase corresponding to reversible reduced expression of NO, which later leads to irreversible nitrergic degeneration (Cellek et al., 2003). In contrast, a prolonged high-fat diet for 20 weeks in C57BL/6 mice led to an increase in nNOS cell bodies in ganglia (Stenkamp-Strahm et al., 2015), suggesting, together with other studies (Adeghate et al., 2003), a probable mechanism of regeneration of nNOS neurons in later stages of diabetes. This adaptive response to diabetes remains to be explored.

In addition to enteric neurons, T2D is characterized by a loss of glial cells through the myenteric and submucosal plexi linked with an increase in oxidative stress (Ferreira et al., 2018). Evidence suggests that changes in the number and morphology of enteric glial cells participate in the gut motility dysfunction observed in diabetic patients (Qi et al., 2013). Determining the exact role of enteric glial cells in the establishment of a diabetic phenotype could represent an attractive solution for researchers to understand the disturbance of the gut-brain axis in response to inflammation and oxidative/nitrosative stress (Ferreira et al., 2018). Reinforcing this hypothesis, supplementation with the antioxidant quercetin restores the number of glial cells in diabetic rodents (Lopes et al., 2012).

Glial cells have now been considered a real active partner of cells constituting the ENS (Seguella and Gulbransen, 2021).

As gut motility is mainly regulated by myenteric neurons, T2D induces altered gut motility as a major pathological hallmark of the disease. In addition to alternate phases of diarrhea/constipation, T2D is characterized by duodenal hypercontractility that favors glucose absorption and modulates the GBA (Chandrasekharan and Srinivasan, 2007). Recently, we identified a novel concept demonstrating that enterosynes, i.e., molecules present in the intestine, can modulate the activity of the "ENS/smooth muscle cells" couple (Knauf et al., 2020). Enterosynes could be nutrients (glucose, lipids, etc.), bioactive peptides released by enterocytes such as apelin (Fournel et al., 2017), neurotransmitters released by the host such as galanin (Abot et al., 2018) or could have a bacterial origin. In this case, modification of gut microbiota by prebiotics has an impact on duodenal hypermotility observed in diabetic mice (Abot et al., 2020). In fact, prebiotic treatment in high-fat diet-fed mice prevents gut hypermotility by modulating the release of 2 novel enterosynes, the bioactive lipid 12-hydroxyeicosatetraenoic acid (or 12-HETE) and enkephalin. After chronic oral treatment, these enterosynes act directly on the expression of nNOS and/or ChAT mRNA in the duodenum to decrease duodenal contractile activity. This is associated with an improvement in the GBA that ameliorates glucose utilization in tissue. Whether these enterosynes are released directly by the gut microbiota and/or by the host *via* a microbial interaction remains to be studied.

Regarding the implication of gut microbiota in the control of glucose metabolism, numerous recent reviews clearly explain its crucial role (Cani, 2019; Gurung et al., 2020; Paone and Cani, 2020; Rastelli et al., 2019; Regnier et al., 2021), and the impact of a considerable number of probiotics is well described. Here, diet is a major contributor to microbiota change, as high-fat diet feeding is associated with gut microbiota alteration in mice, including a decrease in Bacteroidetes and an increase in Firmicutes and Proteobacteria (Cani et al., 2008; Hildebrandt et al., 2009). Recently, it was described that the *Akkermansia muciniphila* abundance is negatively correlated with body weight and is reduced in HFD mice. Daily administration of *Akkermansia muciniphila* to high-fat diet-induced obese mice resulted in decreased weight gain, metabolic endotoxemia, and insulin resistance (Everard et al., 2013). In humans, Depommier *et al*. showed that *Akkermansia muciniphila* supplementation for 3 months improved several metabolic parameters, such as insulin sensitivity, insulinemia and plasma total cholesterol, in overweight and obese volunteers (Depommier et al., 2019), and the beneficial effects were associated with a higher abundance of 2 specific circulating bioactive lipids (1-palmitoyl-glycerol and 2-palmitoyl-glycerol), both belonging to the endocannabinoidome (eCBome). The authors have identified these lipids as endogenous activators of peroxisome proliferator-activated receptor alpha (Depommier et al., 2021). These last articles clearly

show that using targeted approaches with specific bacteria could be considered an innovative approach.

The gut barrier is composed of several chemical and physical components, such as the mucus layer, epithelial cells joined by tight junctions and immune cells (that limit the body's exposure to allergens, pollutants and pathogens) (Regnier et al., 2021). We have recently published a review showing that the gut microbiota is also implicated in the control of gut permeability. In fact, intestinal dysbiosis participates in the transition from a "healthy gut" to a "leaky gut" during metabolic disorders (Regnier et al., 2021). In 2007, our team discovered the concept of metabolic endotoxemia, notably showing that bacterial LPS can reach the circulation to increase tissue inflammation and then participate in the development of insulin resistance (Cani et al., 2007). A high-fat diet increased gut permeability by altering tight junction proteins and intestinal mucus. Regarding the action of LPS on the ENS, Ye *et al*. demonstrated that a high-fat diet increases TLR4 expression in myenteric neurons (Ye et al., 2020). In the same study, the authors showed that the TLR4-LPS pathway stimulates enteric nitrergic neuronal degeneration associated with colonic dysmotility. This last result suggests that microbial factors may have a deleterious impact on the ENS when the gut barrier is disturbed.

In addition, Muller *et al*. (Muller et al., 2020a) identified intrinsic enteric-associated neurons that are sensitive to gut microbiota colonization, particularly in the ileum and colon. These enteric neurons are cocaine- and amphetamine-regulated transcript positive ($CART^+$) and viscerofugal. Colonization of germ-free mice with SPF feces significantly increased the number of $CART^+$ neurons in the distal intestine. Using local retrograde viral delivery, the authors have shown that $CART^+$ neurons displayed innervation of circular and longitudinal smooth muscle and exhibited dense interganglionic patterning. In fact, intestinal $CART^+$ neurons modulate the gut-brain axis to control glycemia *via* a sympathetic ganglion. Ablation of intestinal $CART^+$ neurons is associated with a reduction in blood glucose levels in fasted animals and a significant increase in insulin levels in fasted and fed animals, suggesting that intestinal CART+ neurons control the liver and pancreas. Thus, enteric neurons from the duodenum to the colon could be influenced by gut microbiota signals.

Again, identification of the direct impact of potential beneficial microbes and/or specific metabolites on the ENS and GBA during the establishment of T2D is of crucial importance for novel therapeutic strategies. Despite available treatments, diabetes is still a major world health concern, as global prevalence is predicted to rise to 10.2% (578 million) by 2030 and 10.9 (700 million) by 2045 (Saeedi et al., 2019).

Conclusion

To respond to the question “can we trust the gut?” (Schafer et al., 2020), we could answer “potentially yes”. It seems that there is a clear correlation between ENS dysfunction and the development of a pathologic GBA. Our first medicine could be the modification of food habits to keep our intestine functioning optimally. Nevertheless, if the relation between the ENS and microbiota is altered, we must keep in mind that the restoration of this interaction could be the first step in a potential preventive and/or therapeutic approach(es). Of course, all proposals could be criticized, and we could not totally exclude a pharmacological approach to target the link between the ENS and CNS *via* other enterosynes. At this time, many questions remain unanswered. First, how can all the different messages (neuronal, hormonal and metabolite) from the gut that directly reach the brain (with or without links to gut microbiota) be integrated to treat a specific pathology? The “therapeutic” message from gut bacteria or their metabolites could be driven by the large quantity of intestinal information required to control and treat a physiological function. Researchers have to propose a global approach by combining post-, pre- and pro-biotics (Cani and Knauf, 2021; Cani et al., 2006; Depommier et al., 2019). Second, the majority of GBA pathologies have an intestinal origin. Targeting the brain directly could be a therapeutic option, but the control of side effects could be a challenge. Consequently, the gut will be the more adaptive target to restore the GBA in different disorders. Unfortunately, the situation is more complicated. A recent paper from Borgmann *et al*. (Borgmann et al., 2021) showed the existence of distinct sensory neurons that differentially control metabolic functions such as food intake and glycemia. This last paper opens innovative questions regarding the specific action of microbiota and/or metabolites on intestinal extrinsic neurons to modulate the GBA. Third, due to the degeneration of the ENS and CNS observed during GBA disorders, the better option could be a “preventive” approach rather than a “therapeutic” approach. To conclude, we are only at the beginning of the “gut-brain” axis story, and future challenges have to clearly decipher the relationship between gut microbiota and ENS and its direct consequences on the brain. In addition, the interaction between gut microbiota and the brain is not strictly limited to the ENS, as described in the elegant work by Cryan *et al*. (Cryan et al., 2019). This should also be taken into consideration in understanding physiological mechanisms.

Funding

This study was supported by a grant from the Agence Nationale de la Recherche (ANR) (ANR-18-CE14-0007-01) and by a grant from INSERM (International Research Projects, IRP). P.D.C. is a senior research associate at FRS-FNRS (Fonds de la Recherche Scientifique) and recipient of grants from

FNRS (WELBIO-CR-2019C-02R, “The Excellence Of Science: EOS 30770923”, Projet de Recherche PDR-convention: FNRS T.0030.21).

Declaration of competing interest

P.D.C. and C.K. are cofounders of Enterosys S.A. (Labège, France). P.D.C. is a cofounder of A-Mansia Biotech S.A. (Belgium) and owner of several patents concerning the use of microbiota and health.

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Figures Legends

Figure 1: Structural organization of the ENS. The ENS is organized into 2 plexi: the myenteric and submucosal plexi composed of thousands of ganglia. The cellular network composed of glial cells, interneurons, IPANs, motoneurons, ICCs and muscle cells regulates gut homeostasis (motility, detection of nutrients, etc.). Ach: Acetylcholine; EMN: Excitatory Motor Neuron; ICC: Interstitial Cell of Cajal; IMN: Inhibitory Motor Neuron; IPAN: Intrinsic Primary Afferent Neuron; NO: Nitric Oxide; NT: Neurotransmitter; SCFAs: Short-Chain Fatty Acids; SP: Substance P; VIP: Vasoactive Intestinal Peptide.

Figure 2: Crosstalk between microbiota, enteroendocrine cells, the ENS and the central nervous system. The microbiota communicates directly with enteric neurons and afferent sensory neurons through TLRs or with SCFAs and NTs. The microbiota can also modulate the release of gut hormones whose receptors are on afferent sensory neurons or in the CNS. The gut is under the control of the

ANS since it receives parasympathetic and sympathetic efferences. CCK: Cholecystokinin; CCK1R: Cholecystokinin 1 Receptor; EEC: Enteroendocrine Cell; GLP-1: Glucagon-Like Peptide 1; GLP1R: Glucagon-Like Peptide 1 Receptor; NPYR: Neuropeptide Y Receptor; NT: Neurotransmitter; PYY: Peptide YY; SCFAs: Short-Chain Fatty Acids; TLR: Toll-Like Receptor; 5-HT: Serotonin.

Figure 3: Modification of microbiota composition, neurodegenerative impact on enteric neurons and dysfunction of the GBA associated with diabetes. Diabetes is associated with gut microbiota dysbiosis, including a decrease in *Akkermansia muciniphila* and an increase in Firmicutes and Proteobacteria. Moreover, enteric nitrergic neurons appear to be the most susceptible to diabetic neuropathy, which leads to gut hypercontractility, increased glucose absorption and an alteration of the GBA observed during T2D. Ach: Acetylcholine; EMN: Excitatory Motor Neuron; GBA: Gut-Brain Axis; IMN: Inhibitory Motor Neuron; IPAN: Intrinsic Primary Afferent Neuron; NO: Nitric Oxide; nNOS: Neuronal Nitric Oxide Synthase; SP: Substance P; VIP: Vasoactive Intestinal Peptide.

Fig. 1

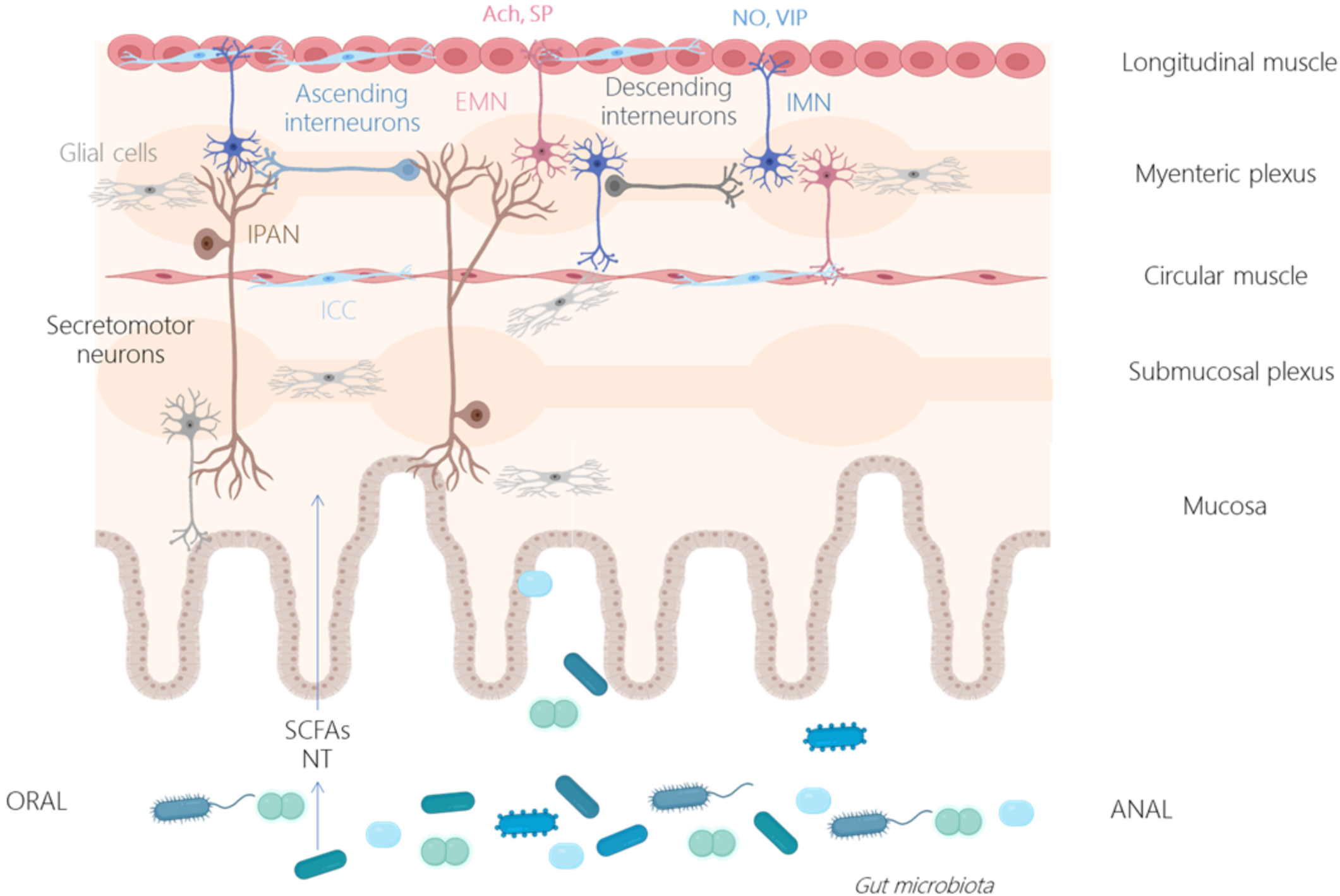

Ach, SP
NO, VIP
Longitudinal muscle
Ascending interneurons
EMN
Descending interneurons
IMN
Glial cells
Myenteric plexus
IPAN
Circular muscle
ICC
Secretomotor neurons
Submucosal plexus
Mucosa
SCFAs
NT
ORAL
ANAL
Gut microbiota

Fig. 2

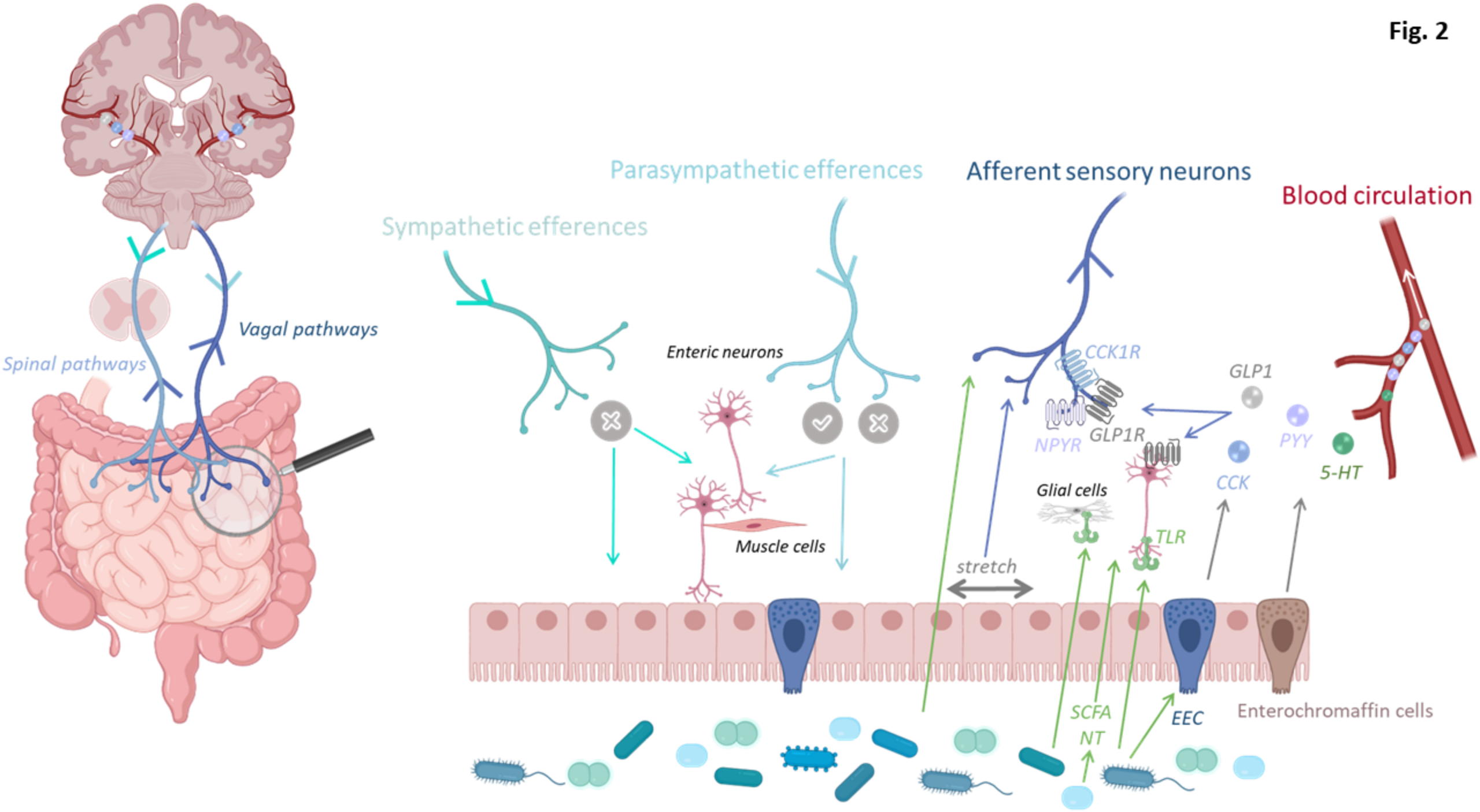
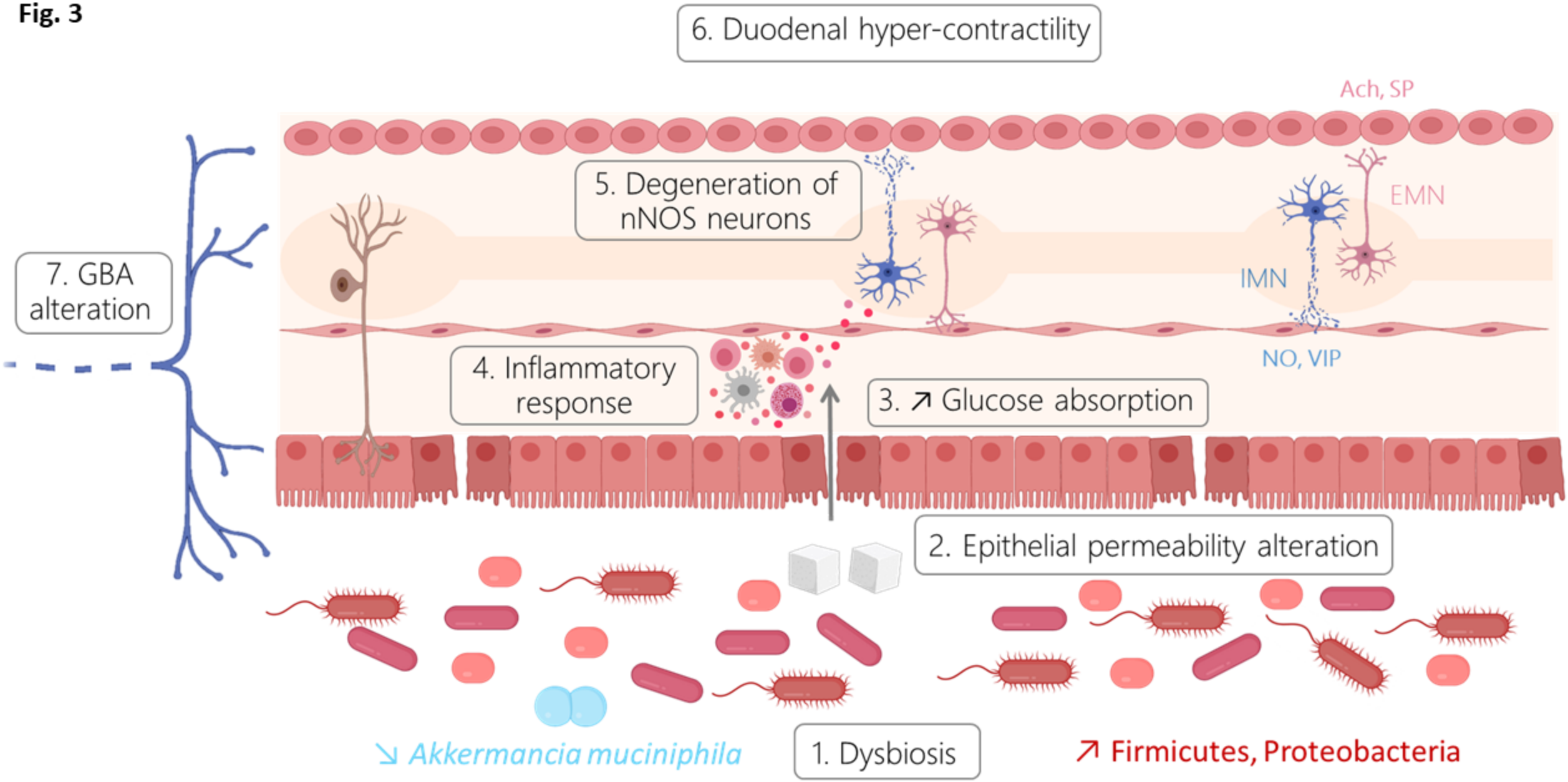

Vagal pathways
Spinal pathways
Parasympathetic efferences
Sympathetic efferences
Afferent sensory neurons
Blood circulation
Enteric neurons
CCK1R
GLP1
NPYR
GLP1R
PYY
5-HT
CCK
Glial cells
TLR
Muscle cells
stretch
SCFA
NT
EEC
Enterochromaffin cells

Fig. 3


6. Duodenal hyper-contractility
Ach, SP
5. Degeneration of nNOS neurons
EMN
IMN
NO, VIP
7. GBA alteration
4. Inflammatory response
3. ↗ Glucose absorption
2. Epithelial permeability alteration
↘ Akkermancia muciniphila
1. Dysbiosis
↗ Firmicutes, Proteobacteria