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Central Control of Gastrointestinal Functions In Health and Disease

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Abstract

Thanks to its extensive intrinsic (enteric) neural networks spanning its entire length, the gastrointestinal (GI) tract has long been recognized for its ability to operate independently of the central nervous system (CNS). Despite that, the CNS provides both sympathetic and parasympathetic inputs to the GI tract, that confers an additional layer of regulation, modulation, and integration over GI functions.

The sympathetic nervous system provides neurovascular control of GI blood flow in addition to its effects to decrease mucosal secretion, regulate sphincter tone, and modulate motility, principally via prejunctional and presynaptic actions. The parasympathetic nervous system, however, exerts both excitatory and inhibitory effects; the extent to which this influences gut functions varies throughout the length of the GI tract. Recent studies have also demonstrated that, in addition to regulation via the autonomic nervous system, ‘higher’ CNS nuclei also provide a significant degree of influence over GI functions under both physiological and pathophysiological conditions

In addition to describing the anatomical neurocircuits and physiological functions of the extrinsic inputs to the GI tract, this review will also discuss the roles of brainstem, midbrain, and cortical nuclei that influence the gut within the context of relevant physiological and pathophysiological conditions.

Graphical Abstract

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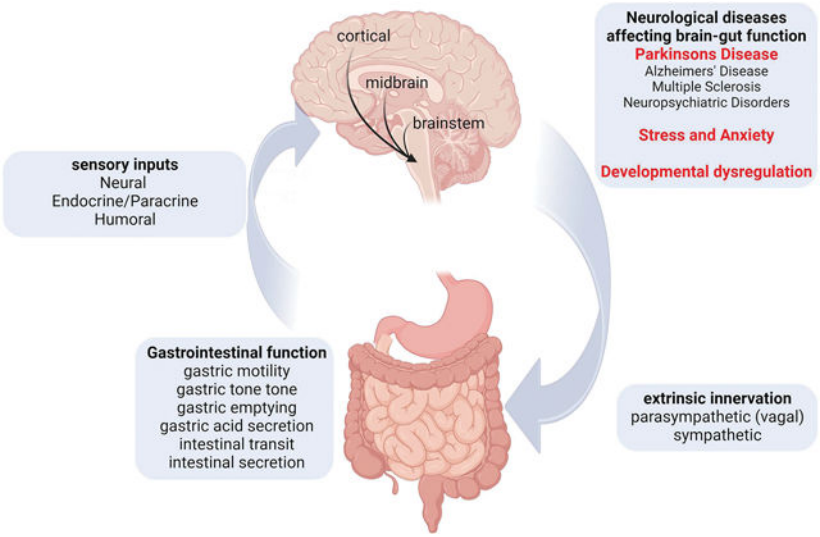

Introduction

The gastrointestinal (GI) tract is responsible for a wide range of complex physiological functions, including digestion, absorption and secretion, co-ordination of motility and transit, plus host defense in response to ingested nutrients, pathogens, and toxins (423). The GI tract, particularly the small and large intestine, is capable of functioning independently (i.e., in the absence of extrinsic inputs), due to the intrinsic enteric neural plexuses that extend along the entire length of the GI tract from the esophagus to the internal and external anal sphincters (137, 423). The intrinsic (enteric) nervous system (ENS), comprising two major nerve plexuses – myenteric and submucosal - endow the gastrointestinal (GI) tract with a significant degree of autonomy and independence over its functions, including digestive processes such as motility, absorption and secretion, transit, and the ultimate elimination of waste (56, 423), indeed the small and large intestines in particular can function almost entirely independently from extrinsic (sympathetic and parasympathetic) neural inputs. In contrast, the esophagus and stomach appear more dependent upon extrinsic innervation which serve to modulate, regulate, and integrate activity to provide a sophisticated degree of “fine tuning” over these autonomic functions (56). The activity and function of these extrinsic inputs is modulated and regulated by brainstem, midbrain, and cortical centers within the brain implying an important overarching influence of cognitive and behavioral functions on the GI tract. Removal of the extrinsic neural inputs to the GI tract causes significant gastric dysfunction and dysregulated motility and emptying, often resulting in symptoms such as nausea, vomiting, abdominal discomfort, bloating, and pain. Surprisingly, however, the much of gastric activity is eventually restored after extrinsic denervation, implying that the ENS alone is sufficient and necessary for the majority of gastric functions.

This review will describe the anatomy and physiology of both parasympathetic and sympathetic innervation to the GI tract, in addition to illustrating the role of major CNS nuclei (brainstem, midbrain, and cortical) that regulate these extrinsic pathways in both

physiological and pathophysiological conditions. Remaining knowledge gaps within the field will be discussed and the potential by which recent technological advances may solve these continuing questions.

Enteric Nervous System

Anatomy, neuronal and neurochemical phenotypes

The enteric nervous system (ENS) is an extensive intrinsic nervous system, that controls several GI functions semi-autonomously (137, 138). In particular, it regulates gastric and intestinal motility, gastric acid secretion, secretive/absorptive functions, local blood flow and barrier permeability as well as interactions with enteric bacteria-endocrine-immune systems contributing to maintenance bacterial-hormonal-immune tolerance(137, 138, 368). ENS neurons located in the submucosa are referred to as forming the submucosal plexus (or Meissner's plexus), while neurons located between the circular and longitudinal muscle layers are referred to as forming the myenteric plexus (or Auerbach's plexus). The ENS, *in toto*, includes enteric neurons, enteric ganglia and their neural connections as well as the nerve fibers that supply effector tissues and enteric glia (138) (Figure 1).

Submucosal enteric neurons can be classified as intrinsic primary afferent neurons (IPANs), interneurons or secretomotor and vasodilator neurons. Indeed, submucosal neurons modulate primarily secretory functions, absorption, and blood flow (138, 477), Conversely, myenteric ganglia contain motor neurons, that innervate the longitudinal and circular muscle layers, with some secretomotor neurons projecting to the mucosa and control GI motility by regulating contractile responses in the muscular layer (420, 422).

Morphological classification identifies different subtypes of enteric neurons, (i) the Dogiel type I that are flattened with short, club-shaped lamellar dendrites and a single axon; (ii) Dogiel type II with multiple axons projecting to other ganglia and mucosa; (iii) Dogiel type III neurons characterized by numerous dendrites that are restricted within the ganglion of origin; (iv) neurons with filamentous dendrites; and, (v) neuronal subtypes with other morphology found throughout the gut or others more restricted in specific gut regions (49, 50).

Electrophysiological classification has divided enteric neurons in two classes: S neurons (morphologically Dogiel type I) that receive fast synaptic input and create actions potentials mediated by tetrodotoxin (TTX)-sensitive sodium channels and followed by a short duration afterhyperpolarization, and AH neurons (morphologically Dogiel type II) with a prolonged afterhyperpolarization (139) and action potentials only partially blocked by TTX, and characterized by currents mediated by voltage-gated sodium and calcium channels. Based on these classifications, Dogiel type II neurons are regarded mainly as intrinsic primary afferent (intrinsic sensory) neurons while Dogiel type I are motoneurons and interneurons, although it is noteworthy to point out that all enteric neurons are multifunctional (137, 140, 186, 187, 425).

Of note, enteric neurons release different neurotransmitters, including acetylcholine (Ach), vasoactive intestinal peptide (VIP), dopamine, substance P (SP), calcitonin gene-related

peptide (CGRP), 5-hydroxytryptamine (5-HT), nitric oxide (NO) that, in turn, influence enteric motor and secretory/absorption functions, immune/inflammatory/endocrine cell activity and/or modulate intestinal barrier functions and integrity (132, 287).

Enteric Glial Cells

Enteric glial cells [glial fibrillary acidic protein ($GFAP^+$), proteolipid protein 1 ($PP1^+$), $nestin^+$, S100 calcium-binding protein B ($S100\beta^+$) and sex determining region Y box-containing gene 10 ($Sox10^+$)] are located in submucosal and myenteric plexuses as well as in the mucosa layer in close proximity to epithelial cells (115, 481). Based on enteric glial cell morphology and localization within the GI tract, these glial cells are classified into (i) intraganglionic: located in the enteric ganglia and characterized by star-shaped resembling protoplasmic astrocytes; (ii) interganglionic: with long, slender processes resembling fibrous astrocytes and associated with nerve fibers in the interganglionic stroma; (iii) mucosal: characterized by long and branched processes in contact with nerve fibers and epithelium and; (iv) intramuscular: cells are bipolar and elongated (107).

Enteric glia interacts with enteric neurons as well as with epithelial and immune cells contributing to neurogenesis, neuroprotection and neurotrophism, GI motility, mucosal barrier integrity and immune/inflammatory responses (106, 107). For instance, enteric neurotransmitters or neuromodulators, including acetylcholine and purines, can promote the increase in glial cytosolic Ca^{2+} release with consequent release of gliotransmitters, such as adenosine triphosphate ATP and γ-Aminobutyric-acid (GABA), via either the glial connexin 43 (Cx43) hemichannel or neurotransmitter transporters. Such release has been found to contribute to the maintenance of ENS organization and functions (40, 313). Indeed, alterations of glial $Ca2^+$ levels have been found to be associated with the onset of GI motor disturbances, such as chronic constipation and Disorders of Gut-Brain Interaction (DGBI) such as functional dyspepsia (25, 89). Of note, enteric glia-neuronal interplay is also mediated by Toll like receptors (TLR) receptors expressed on both cell subtypes, whose activation by microbe- or pathogen-associated molecular patterns (MAMPs or PAMPs) can influence ENS neurochemical phenotype and functions (76)a(81, 248). Mucosal glia contribute to the maintenance of gut barrier integrity and functions in physiological conditions as well to barrier impairments in inflammatory/metabolic disorders, through the release of neurotrophic factors or inflammatory mediators respectively, such as 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), glial cell line–derived neurotrophic factor (GDNF), proepidermal growth factor and interleukin-1beta(106, 510). In addition, mucosal glia is associated with the enteroendocrine cell neuropod, involved in the modulation of sensory signal transduction from the gut to the brain through extrinsic vagal innervation (218). Intraganglionic enteric glial cells participate actively in gliogenesis and neurogenesis as well as neuroprotection and neuronal activity (13, 29). Enteric glia also interacts with immune/inflammatory cells, driving the polarization of muscularis macrophages towards pro-inflammatory phenotype that in turn, influence gut motility (10, 163, 466).

Intrinsic vs Extrinsic Regulation of GI functions

GI functions are regulated by reciprocal neuronal connections between the ENS and the CNS (56, 302). The neuronal cell population of ENS, including intrinsic primary afferent

neurons (IPANs), interneurons, viscerofugal, motor neurons and secretomotor neurons, regulates several GI functions such as motility, fluid exchange, absorption/secretion, and blood flow (138). In particular, the myenteric plexus controls GI motility through the regulation of contractile motor responses in the longitudinal and circular muscles, while the submucosal plexus regulates secretion/absorption, intestinal permeability and blood flow, through different enteric motor and secretory pathways, including enteric cholinergic, nitrergic, tachykininergic, dopaminergic, serotoninergic and VIP-expressing nerves (88, 334, 396, 420, 422, 477).

Enteric neurons also communicate with extrinsic sympathetic and parasympathetic neuronal pathways to modulate GI functions (see below) (285). Sympathetic inputs to the gut tonically regulate secretion and motility and secretion, in particular, is regulated by a direct postsynaptic input to enteric secretomotor neurons (285), while motility is modulated by indirect presynaptic inputs that inhibit enteric neuronal activity (138). Indeed, sympathectomy increases GI secretion while either direct stimulation of sympathetic nerves or exogenous application of NE increased fluid absorption (56). The indirect inhibitory effects of sympathetic pathways on gut motility result from the reduced release of excitatory neurotransmitters such as acetylcholine from enteric neurons rather than from a stimulatory effect on nitrergic inhibitory neurons (350, 513).

In general, the effects of sympathetic activation on the GI tract occurs via spinal reflexes in response to stimulation of the gut or through other mechanisms such as painful (nociceptive) stimuli, although other sympathetic reflexes - regarded as intestino-intestinal sympathetic reflexes - have been identified and involve viscerofugal enteric neurons. In particular, viscerofugal enteric neurons activate sympathetic postganglionic neurons in the abdominal prevertebral ganglia bypassing the CNS allowing, for example, feedback from intestinal distal regions to slow propulsion in more proximal regions of the gut (513). These findings suggest that sympathetic inputs differentially influence enteric neuronal activity to alter GI motility and secretion (419). For instance, the the difference in sympathetic innervation from the proximal to the distal gut prevents the anterograde movement of fecal content in the distal colon and decreases the reflex-initiated propulsive contractions in the proximal colon.

Sympathetic neurocircuits also innervate enteric glial cells; under pathological conditions, enteric glia respond to ATP and NE released by sympathetic fibers resulting in increased enteric glia reactivity and gliosis. Supporting this view, a recent study reported that, following intestinal manipulation to induce post-operative ileus (POI) in mice, the activation of sympathetic adrenergic signaling triggered enteric glial reactivity and acute gliosis (267).

As discussed below in more detail, besides the extrinsic sympathetic innervation, an extensive vagal efferent innervation throughout the GI tract (up to the splenic flexure) regulates several functions, including esophageal and gastrointestinal motility and secretion throughout the GI tract, as well as anti-inflammatory effects in the lower GI tract (309, 467) while lumbosacral parasympathetic inputs to the descending colon are involved in the regulation of colonic motility and defecation (17, 216), discussed in more detail below.

In recent years, a vagal cholinergic anti-inflammatory pathway has been identified that exerts anti-inflammatory and modulatory effects on the immune system reducing intestinal inflammation (308, 309). In particular, the vagus nerve innervates enteric cholinergic nerve fibers located in close proximity to intestinal muscularis macrophages. In this context, the stimulation of vagal efferents activates enteric cholinergic nerve fibers that, in turn, release acetylcholine interacting with α7 nicotinic acetylcholine receptors (α7nAChRs) that induce the polarization of muscularis macrophages towards anti-inflammatory phenotype. In particular, the vagus nerve exerts anti-inflammatory effects via activation of α7nAChRs-Jak2-STAT3 signaling that, in turn, decreases the release of proinflammatory cytokines (112, 309). Indeed, vagotomy accelerates the onset and the severity of inflammation in mice during the first and second, but not the third, cycle of dextran sulphate sodium administration (149), suggesting that the vagus exerts protective effects in the first phase of bowel inflammation.

The ENS also interacts with primary afferents with spinal and vagal afferents that are involved in the maintenance gut homeostasis through the regulation of motility, secretion, blood flow, defense, mood, digestive reflexes, hunger/satiety balance, or pain sensation (164, 235, 237, 298, 362). The cell bodies of vagal afferent neurons are located in the nodose ganglia and receive inputs from ENS neurons located throughout the GI tract (see below). Of those afferent terminals, intraganglionic laminar endings (IGLEs) have been shown to be multimodal in terms of their responsiveness, including the ability to respond to neurotransmitters or neuropeptides (364). Vagal afferent terminals also innervate smooth muscle, mainly in the stomach, where vagal fibers course parallel to the muscle fibers and in close association with Interstitial Cells of Cajal (ICCs), as well as mucosal layer where free nerve endings course throughout the length of the GI tract (358). The myenteric plexus also contains arborizations originating from spinal afferents whose cell bodies are located in dorsal root ganglia. These spinal afferent nerve endings are located in the circular muscle, submucosa, and mucosal layers of the gut (422).

SIP syncytium and regulation of motility and secretion.

Besides neurogenic control, a myogenic apparatus involved in the regulation of colonic motility involving the unique interconnectivity, interplay and communication between **S**mooth muscle cells, the **I**nterstitial cells of Cajal (ICC), and **P**latelet-derived growth factor receptor α positive (PDGFRα+ cells has been described (398). Due to the close proximity of these cell types, termed the **SIP** syncytium, they function as a cellular network that regulates smooth muscle activity and contractility, The ICCs (c- KIT^+, $TMEM16A/ANO1^+$ and $vimentin^+$) are stellate cells located along the submucosal surface of colonic circular muscle bundles (ICCs-SM), in the myenteric plexus (ICCs-MY) and intramuscularly (ICCs-IM) in the esophagus, stomach, small intestine and colon. They are considered pacemaker cells involved in the regulation of GI motility as well as in the interplay between enteric neurons and smooth muscle cells (138).

ICCs have an abundance of mitochondria, a moderately developed Golgi, caveolae, and rough and smooth endoplasmatic reticulum. The $PDGFR\alpha^+$ cells, regarded as “fibroblast-like” cells ($vimentin^+$), lack caveolae and basal lamina, are typically less electron dense

and have an abundance of rough endoplasmic reticulum compared to ICCs. These syncytial interstitial cells are electrically coupled via gap junctions that facilitate communication among all SIP cells (398). SIP cells display unique expression patterns of neurotransmitter receptors, second messenger pathways, $Ca2^+$ handling mechanisms and ion channels, and they are closely associated with enteric motor neurons (395). Indeed, ICC-generated spontaneous pacemaker activity stimulates smooth muscle cells and generates electrical slow waves and phasic contractions throughout the GI tract. In parallel, enteric inhibitory nitrergic and purinergic neurotransmissions in the proximal or distal colon, respectively, as well as extrinsic neural inputs stimulate ICC and PDGFRα$^+$ cells, respectively, to conduct to smooth muscle cells and to modulate motor responses (239, 252, 274).

The stimulation of ICC and PDGFRα$^+$ cells is associated with opening of signature $Ca2^+$-activated Cl^- channels, ANO1 or $Ca2^+$-activated K^+ channels (SK3), respectively. The specific channel opening results in spontaneous transient inward currents (STICs) that, via promoting spontaneous transient depolarizations (STDs) or spontaneous transient hyperpolarizations, modulate the baseline membrane potential (196). In this context, recent studies have demonstrated that the ongoing discharge of spontaneous transient depolarizations or hyperpolarizations by ICC and PDGFRα+ cells, respectively, exerted conditioning effects on membrane potentials in the SIP syncytium with consequent modulation of the excitability of SMCs (196). In addition, the purinergic-mediated hyperpolarization in PDGFRα^+ cells, being electrically coupled to ICC, elicited the inactivation of CaV3 channels and promoted Ca^{2+} entry into ICC via anode-break upon cessation of inhibitory stimuli (240). These findings suggest that SIP syncytium cooperates in an integrated manner to influence motility behavior.

Highlights:

- The enteric nervous system (ENS) is a separate and distinct branch of the autonomic nervous system and is comprised of interconnected neural networks termed myenteric and submucosal plexuses
- The myenteric plexus, located between the circular and longitudinal muscle layers, is involved principally in regulation of motility
- The submucosal plexuses, located between the muscularis mucosa and circular muscle layer, is involved principally in regulation of secretion/absorption
- Enteric neurons can be classified by their electrophysiological, morphological, and neurochemical phenotypes
- Glial cell subtypes are located in the mucosa (close to epithelial cells), the submucosa, myenteric plexus, and muscle layers
- The neural plexuses contained within the enteric nervous system (ENS) allow the GI tract to function independently of extrinsic (sympathetic and parasympathetic) control. The extent of sympathetic or parasympathetic regulation is non-uniform thoughout the GI tract

- The sympathetic nervous system provides neurovascular control of GI blood flow and modulates secretion, sphincter tone, and motility (indirectly)
- The parasympathetic nervous system exerts both excitatory and inhibitory effects on GI motility and transit, as well as modulation of acid secretion
- The gut microbiome modulates gut-brain signaling directly and indirectly, via neural, endocrine, and immune pathways
- Loss of enteric neurons, particularly inhibitory NOS neurons, is associated with GI dysmotility in aging, obesity, and diabetes (83, 426, 427, 507)

Vagal sensory afferent innervation of the GI tract

At the peripheral level, the vagus nerve is a mixed sensory:motor nerve, comprised of between 60–80% sensory fibers (species dependent) with the remainder being motor (see (113, 346) for review). Vagal afferent neurons that innervate the subdiaphragmatic viscera lie within the paired nodose ganglion (or nodose-jugular ganglion complex). Neurons are pseudounipolar, with an initial axon segment, or stem, extending from the cell body before it bifurcates into two axons, one of which terminates peripherally and the other projecting centrally and entering the brainstem via the tractus solitarius (TS). At the level of the caudal hindbrain, however, the sensory and motor fibers diverge, with sensory inputs entering the brainstem more dorsal to the efferent motor output. Afferent terminals may also project to, or terminate within, the area postrema (AP), however, as well as the dorsal motor nucleus of the vagus (DMV). Indeed, a monosynaptic vagal afferent input that projects to the DMV regulates the presynaptic ‘state of activity’ of NTS-DMV inhibitory GABAergic terminals and plays a critical role in physiological neuroplasticity within this synapse ((380)see below). Neurons within the smaller jugular ganglion arise from the neural crest, and innervate the pharynx, larynx, esophagus, and lower airways whereas nodose ganglion neurons arise from the placode, and innervate the viscera (372). While there is no clear viscerotopic organization of afferent cells bodies within the nodose ganglia, neurons innervating distinct organs tend to be non-overlapping suggesting organ-specific information may be encoded within the nodose ganglion but a viscerotopic map is less obvious if present at all (4, 520).

Vagal afferent neurons can be classified by a variety of difference means, including neurochemical phenotype, anatomy (region of GI tract innervated), response to distension or pressure (low or high-threshold), receptive field (mucosa, muscular, or mesenteric), stimulus modality such as mechanical, osmotic, and chemical stimuli as well as responding directly to some macronutrients, as well as responding indirectly to ingested nutrients via neuropeptides and neurohormones released from enteroendocrine cells (EEC) (111, 161). Importantly from an integrative physiological perspective, however, many vagal afferents are polymodal and respond to a range of different stimulation parameters (490)..

As specialized endocrine cells located within the GI tract, EEC release GI neurohormones and neuropeptides in response to distinct intraluminal stimuli; K cells, for example, release gastric inhibitory peptide (GIP) in response to intragastric glycogen, I cells secrete

cholecystokinin (CCK) in response to bile salts and fat, and L cells release glucagon-like peptide 1 (GLP-1) and GLP-2, peptide YY (PYY), and oxyntomodulin, and) in response to glucose (111, 161). In addition to paracrine responses to released EEC neurohormones and neuropeptides, vagal and DRG afferents can also respond directly to EEC activity, through fast synaptic connections with specialized EEC, termed neuropods (171, 218). EECs are electrically excitable cells, capable of modulating their activity in response to intraluminal contents such as ingested nutrients. Intraluminal nutrients including glucose, for example, increases L cell excitability via both closer of ATP-sensitive potassium channels (in response to glucose uptake via the sodium glucose transporter, SGLT1) as well as activation of transient receptor potential channel 5 (TRPM5) following activation of the G-protein coupled sweet taste receptor, T1R2/3, an increase in intracellular calcium resulting in membrane depolarization and calcium influx via voltage sensitive calcium channels (116, 241, 299) The increased intracellular calcium in neuropods activates synaptic transmission to vagal afferent terminals, increasing afferent transmission centrally. Activation of vagal afferents via fast synaptic transmission appears important in central reward signaling (34, 171) while the relatively slower paracrine activation of vagal afferent may be more important in more sustained satiety signaling.

Genetic approaches have also identified distinct vagal afferents that respond to either mechanical stimulation or ingested nutrients either directly or indirectly. Vagal afferent neurons expressing GPR65, for example, innervate the proximal small intestine, respond to serotonin, are activated in response to ingested nutrients, and have central projections that terminate within the commissuralis NTS. In contrast, vagal afferents expressing the GLP-1 receptor (GLP-1R) gene display characteristics of gastric stretch mechanoceptors, respond to gastric stretch, and have central projections that terminate within the medial NTS (496). That genetic techniques can be used to identify such discrete vagal afferent subpopulations gives support to previous anatomical and functional studies describing a “labeled line” theory of gut-brain (and higher) signaling, such that vagal afferent specialized for specific sensory modalities and functions terminate on NTS neurons that are also specialized in terms of their neuronal properties and projection targets.

Notably, vagal afferent neurons display a significant degree of plasticity (233; Figure 3); the sensitivity and responsiveness of vagal afferent neurons is altered by feeding cycles with, for example, gastric mechanoreceptors in the mouse being more sensitive during the resting light phase and less sensitive during the active dark phase when the majority of food is consumed (234). Vagal afferents also display circadian oscillations (230), and these cyclical variations in afferent sensitivity are ablated by exposure to a high fat diet, or diet induced obesity (232, 234). Gastric vagal afferents also show alterations in their responsiveness and sensitivity in response to the body’s nutritional status, with the sensitivity of tension-responsive afferents decreasing following fasting (i.e., greater meal size required to signal satiation (229), The distribution of receptors on the cell surface of vagal afferent neurons (hence their ability to respond to neurochemicals and neuromodulators) is also altered by nutritional status, with neurons displaying an “anorexigenic” or “orexigenic” phenotype, depending on feeding or fasting (118, 231). Similarly, altered energy demand can modulate vagal afferent functions with, for example, the increased energy demands – hence increased food intake – in response to pregnancy is accompanied by a decrease in sensitivity of gastric

tension-sensitivity afferents (271). Likewise, exposure to high fat diet (108, 229, 231, 234) decreases vagal afferent sensitivity which may contribute to ingestion of larger meals and the development of obesity.

Spinal afferent innervation of the GI tract

Spinal afferent (sensory) neurons innervating the GI tract, whose cell bodies lie within the dorsal root ganglion, enter and terminate within the thoracic spinal cord (T1–13). Anatomical tracing studies have identified several spinal pathways by which this information is relayed centrally, including the spinosolitary, spinohypothalamic, spinoparabrachial, spinomesencephalic, and spinotelencephalic tracts, whose projections terminate within the NTS, hypothalamus, parabrachial complex (PB complex). Periaqueductal gray (PAG), and amygdala, respectively (71, 72, 80, 280, 318). Interestingly, many of these areas also receive indirect inputs from parasympathetic (vagal) pathways, implying that integration of GI inputs occurs are multiple levels throughout the CNS and not just at the level of the NTS within the brainstem.

Spinal afferent neurons and pathways are well recognized as relaying nociceptive, inflammatory, or noxious information centrally, but these sensory neurons are also responsive to innocuous information, including low pressure distention, mucosal stroking, and circumferential stretch or distension (203, 356, 376, 518). In contrast, while traditionally being considered as relaying innocuous homeostatic information centrally, vagal afferents can also respond to high pressure distention into the nociceptive range (204, 205, 456–458). By consequence, while predominantly relaying specialized sensory information, both vagal and spinal afferents can relay all types of sensation (innocuous and noxious). Together with the convergence of vagal and spinal afferent inputs within the NTS, this implies a considerable degree of overlap in information processing, as well as allowing the possibility for vagal afferents to nociceptive inputs while spinal afferents can modulate vagal control of the upper GI tract.

Anterograde labelling of mouse lumbosacral DRG neurons identified a remarkably diverse and complex set of distinct morphological types of afferent endings in the submucosa, myenteric plexus, and circular muscle of the colon, as well as blood vessels within the intestine. The majority of afferent projections enter the colon through the serosa (but do not terminate within the serosa), and travel for variable distances before terminating within the colon. Notably, terminal fields were identified within all layers of the colon including mucosa and multiple morphological phenotypes (simple, branching, and complex) were identified in myenteric and submucosal plexuses as well as the circular muscle (424). More recent genetic approaches uncovered five different phenotypes of DRG sensory neurons innervating the GI tract. All types (*TrkB+, Th+, Adra2a+, Bmpr1b+.* and *Sstr2*+) innervated the myenteric plexus, with some phenotypes additionally innervating the mucosa (*Sstr2*+), the submucosal plexus (*Sstr2+, Adra2a*+) and circular muscle (*Th*+). Interestingly, the *TrkB*+ afferent endings have the lowest threshold for activation by distention with a response latency that identifies them as Aδ (unmyelinated) fibers. *Th*+ afferent endings, in contrast, also respond to low threshold distension but are slowly adapting C-fibers, while *Bmpr1*+ afferents are also slowly adapting but respond to high threshold distention and

are identifiable as high threshold Aδ fibers. Curiously, ablation of these *Bmpr1*+ endings prolonged colonic motility suggesting a role in ongoing physiological functions (500).

Microbiome modulation of gut-brain functions

In addition to actions to modulate the ENS, the gut microbiota has also been found to modulate CNS physiology, both directly or indirectly, through neuronal, endocrine and immune pathways (148, 343). In particular, gut microbiota and their metabolites can interact with sympathetic and parasympathetic systems and, in turn, affect central circuits, including behavior (66, 103, 298).

With regard the parasympathetic signaling, the afferent (or sensory) vagus nerve is the main extrinsic input (see below) influenced by gut microbiota through both the activation of enteroendocrine (EECs) and enterochromaffin cells (ECCs) as well as sensing bacterial metabolites directly (42). For instance, beneficial bacteria metabolites, including short chain fatty acids (SCFAs), such as butyrate, acetate and propionate, promote serotonin release from EECs, that, in turn, modulate the activity of vagal afferent nerve fibers, both directly in a paracrine manner as well as indirectly, through synaptic connections between vagal afferent terminals with neuropod-like extensions from EECs (41, 375, 506) (see above). Neuropod-vagal afferent synaptic signaling appears to have implications beyond intraluminal nutrient sensing, however. In the mouse colon, flagellin (the proteins that form the hollow cylinder filament in flagellated bacteria) stimulate toll-like receptor 5 (TLR5) in PYY-containing neuropods. The subsequent PYY release activates neuropeptide Y 2 receptors (NPY2R) on vagal afferents to increase vagal afferent firing and decrease food intake (281). In parallel, microbiota-derived serotonin, despite not crossing BBB, influence brain physiology by activating 5-HT3 and 5-HT4 receptors on vagal ascending nerve fibers (42, 354)

SCFAs also activate their receptors, including G protein-coupled receptor 41 (GPR41), also referred to as free fatty acid receptor 3 (FFAR3) on sensory ganglia, suggesting a possible interaction with primary afferent transient receptor potential vanilloid 1-positive ($TRPV1^+$) neurons. There is also evidence that vagal afferents can be stimulated directly by *Lactobacilli* in the upper intestine to modulate the hypothalamus-pituitary-adrenal (HPA) axis and anxiety (282, 355) or indirectly through glucagon-like peptide-1 (GLP-1) secretion from enteroendocrine cells (68). The mechanisms underlying the direct gut microbiota-vagus nerve interplay rely mainly on TLRs, in particular TLR-4 (172, 210). Of note, a recent study reported that mice depleted of gut microbiota following antibiotic cocktail treatment displayed hypolocomotion and increased levels of GLP-1; both the pharmacological block of GLP-1 receptors as well as subdiaphragmatic vagotomy rescued the deficient locomotor phenotype in microbial-depleted mice. Moreover, colonizing *Lactobacillus reuteri* and *Bacteroides thetaiotaomicron* in microbiota-deficient mice has been found to decrease GLP-1 levels and to restore the hypolocomotor phenotype. These results suggest that specific gut microbes modulate motor behavior via enteroendocrine and vagal dependent neural pathways (255). Supporting these results, vagotomy in mice has also been found to inhibit the central effects of *Lactobacillus* and *Bifidobacterium* strains, with consequent alterations in mood and behavior (30, 48). In parallel, autonomic nervous system inputs can

activate ECCs to release serotonin into the gut lumen, that, in turn, influences gut microbial composition and functions (410). Microbial-products, including SCFAs and tryptophan can also spread through gut vascular barrier and reach the brain directly influencing CNS functions (300). SCFA, particularly butyrate, have shown promise in the treatment of anxiety and depression in animal models (475) while patient studies have suggested associations between reduced stress and anxiety following colon-delivered SCFA (67). However, given the short half-life of SCFAs, further studies aimed at investigating the spreading of SCFAs to the brain need to be implemented (82).

Gut microbiota influences also gut-extrinsic sympathetic innervation (see below) through a gut-brain circuit (325). In particular, the depletion of gut microbiota in mice is associated with an increased cFos (as a surrogate marker for neuronal activity) expression in sympathetic premotor neurons within the celiac and superior mesenteric ganglia, while the colonization of germ-free mice with SCFAs–producing bacteria suppressed cFos activity (325). In this same study, the authors identified a subset of distal intestine-projecting vagal neurons that are positioned to have an afferent (sensory) role in microbiota-mediated modulation of gut-related sympathetic neurons. In addition, retrograde polysynaptic neuronal tracing from the intestinal wall showed, following microbial depletion, the activation of brainstem neurons as well as of efferent sympathetic premotor glutamatergic neurons that regulate GI transit (dorsovagal complex, DVC and rostroventrolateral medulla (RVLM), see below)(325)}. Indeed, germ-free mice have been found to have an increased extrinsic sympathetic activity and slowed GI motility while transfer of feces from specific pathogen–free donors to GF mice normalizes sympathetic activity (325). These findings suggest a gut microbiota-mediated control of extrinsic sympathetic nervous pathway activation through a gut–brain circuit.

Brainstem integration of sensory afferent inputs

Vagal afferent neurons innervating the subdiaphragmatic viscera send their central projections via the tractus solitarius to terminate in a somewhat viscerotopic manner within NTS subnuclei (4, 51). Inputs from the GI tract innervate neurons within the gelatinosus, commissuralis, and medialis subnuclei, while esophageal afferents terminate within the centralis subnucleus. The morphology of NTS neurons is such that their dendrites project extensively across the nucleus, however, including projections to the contralateral commisuralis and medialis NTS (220, 335), hence extensive intermingling occurs between dendrites of neurons involved in distinct autonomic (cardiovascular, respiratory, GI) providing a means by which autonomic and homeostatic reflexes can be co-ordinated across organ systems. It should be noted that the NTS also receives sympathetic afferent inputs directly via the spino-solitary tract and, as a result, is one of the few (if note the only) CNS nuclei to receive inputs from vagal and sympathetic afferents potentially allowing direct integration of interoceptive (vagal) with nociceptive (sympathetic) information.

While vagal afferent neurons themselves display a variety of different neurochemical phenotypes, glutamate is the major neurotransmitter used at the afferent-NTS synapse (8, 9). The role for non-glutamatergic signaling is still somewhat controversial; while most, if not all, afferent reflexes can be blocked or attenuated by brainstem application of glutamate

receptor antagonists, NTS neurons display a plethora of (functional) receptors, many of them for neurotransmittersor neuromodulators contained within vagal afferent neurons, several of which have been shown previously to modulate NTS neurons and autonomic reflexes (346). The most conservative explanation would suggest that afferent released neurotransmitters/modulators may modulate the actions of afferent-released glutamate, as has been proposed for cocaine and amphetamine regulated transcript (CART) and melanin concentrating hormone (MCH) which exert opposing effects on food intake (114). Glutamate may exert effects at the level of the NTS through a variety of receptors, with non-NMDA (AMPA), NMDA, and all three groups of mGluR being present and having functional roles (7, 9, 43, 152–154, 519). While glutamatergic signaling is mediated predominantly, if not exclusively, via activation of AMPA receptors, NMDA receptor activation occurs following higher frequency stimulation, presumably as a means to maintain synaptic efficacy and signal throughput (519). While, notably, the release probability for glutamate at the afferent-NTS synapse is extremely high (~90% under ex vivo slice electrophysiology conditions), glutamate can be released from vagal afferent terminals by spontaneous, synchronous, and asynchronous mechanisms. Synchronous (or action potential dependent) co-ordinated release is important for signal fidelity and the patterning of afferent signaling (370). In contrast, asynchronous release is less strictly associated with action potential firing and appears important under higher stimulus frequency rates when AMPA receptors desensitize and NMDA receptor mediated signaling is important for the maintenance of synaptic throughout (519). Most afferent-NTS transmission occurs, however, through spontaneous (action potential independent) release of glutamate (130, 502) but the “tone” or rate of this spontaneous release is subject to modulation including by, for examples, feeding peptides like CCK (14) as well as autonomic and circadian rhythms (370, 371).

Parasympathetic innervation and control of the upper gastrointestinal tract

Parasympathetic innervation to the stomach, small intestine and proximal large intestine (proximal colon in rodents, and ascending and transverse colon in humans) is supplied by the vagus nerve. Anatomical studies, including retrograde and anterograde tracing studies as well as more recent genetic labeling studies, have demonstrated that the preganglionic neurons that provide efferent vagal innervation to the stomach, small intestine, and proximal large intestine arise from the dorsal motor nucleus of the vagus (variously termed DMV, DMNV, or DMX as the vagus is the 10th cranial nerve) within the brainstem (5, 6, 411).

The density of vagal efferent innervation decreases distally through the intestine, with the stomach in particular receiving particularly dense innervation (33). Notably, in species in which the esophagus is composed of smooth muscle (cat, rabbit, ferret, human) vagal innervation also arises from neurons of the DMV. In contrast, innervation to striated esophageal muscle (rat, mouse) arises from neurons in the Nucleus Ambiguus (N.Amb), as does innervation to the to the pharynx and larynx (both compact and external formation) (51, 209).

Vagal efferent motoneurons

Of all preganglionic parasympathetic neurons innervating the viscera, those within the DMV have proven most tractable for detailed study and investigation, both anatomically and physiologically, although it should be noted that the anatomical location of DMV neurons has presented challenges in making recordings in freely moving rodents because of the potential damage to the more dorsally located nucleus tractus solitarius (NTS) with the resulting compromise of essential cardiorespiratory functions, or damage to the cerebellum and the potential compromise of motor and autonomic functions (see below although also note (119).

Anatomically, retrograde tracing studies have shown that DMV neurons appear to be organized into ‘longitudinal columns’ spanning the entire rostro-caudal extent of the nucleus, that correspond to one of the five efferent branches of the vagus nerve through which the cell bodies send their axonal projections (134, 337, 363) (Figure 2). Detailed cell counting suggests DMV neurons have axonal projections that are restricted to one vagal nerve branch, with limited evidence of collateral projections through additional efferent branches. Each side of the bilateral DMV contains a ‘column’ of cell bodies that are located within approximately two-thirds of the medial nucleus and that project via the gastric branches of the vagus (left DMV, anterior gastric branch innervating the ventral stomach; right DMV, posterior gastric branch innervating the dorsal stomach; Figure 4).

The lateral tips of each bilateral DMV contain a column of neurons that projects via the celiac branches of the vagus (left DMV, accessory celiac; right DMV, celiac). The final – hepatic – branch, is contained within the medial left DMV, overlapping to some extent with neurons of the anterior gastric branch. As predicted, perhaps, from the need for detailed integration and the intricate control of physiological functions, the peripheral projections of these DMV neurons show far less segregation and their innervation targets show more integration; the stomach, for example, receives innervation from both gastric branches, the colon receives innervation from both the celiac and accessory celiac branches, while the duodenum receives innervation from all five vagal branches (33). Thus, each GI regions receives input from both the left and right brainstem although the density of this innervation decreases in a distal direction; it appears that essentially every myenteric neuron within the stomach receives vagal efferent innervation which decreases to around two thirds of neurons in the cecum, and one fifth of neurons in the colon. (33, 84).

As a consequence of their preganglionic nature, DMV neurons have a cholinergic phenotype, as evidenced by the presence of choline acetyltransferase (ChAT) - the enzyme responsible for producing acetylcholine - which has been demonstrated immunohistochemically within virtually all DMV neurons, and release acetylcholine to activate nicotinic receptors on postganglionic neurons and targets located within the GI tract including interstitial cells of Cajal (ICC) and myenteric neurons (397). Immunohistochemical studies have shown the presence of additional neurotransmitters within DMV neurons, notably catecholamines (within the A2 area) and nitric oxide (NO) (166, 197, 219, 251, 275). Notably, however, all vagal efferent induced responses are blocked by nicotinic antagonists (406) and stimulation of vagal efferent axons induced

only nicotinic cholinergic responses in postganglionic targets cells. At the postganglionic levels, either an excitatory (cholinergic; muscarinic) or inhibitory (non-adrenergic, non-cholinergic (NANC) predominately NO or vasoactive intestinal polypeptide (VIP) mediated) response can be elicited, that is, vagal efferent stimulation can either increase or decrease gastrointestinal tone and/or motility depending upon the type of postganglionic target (56). The majority of studies investigating GI motility have suggested that the efferent cholinergic pathway is active tonically, i.e., inhibition of postganglionic cholinergic (muscarinic) responses via systemic administration of atropine induces a profound gastric inhibition, whereas less evidence exists to suggest tonic ongoing activity within the inhibitory NANC pathway (56). Gastric relaxation or gastroinhibition can, and does, result from either inhibition (withdrawal) of the excitatory cholinergic pathway or activation of the inhibitory NANC pathway. It should be noted, however, that the majority of these studies have been carried out in anesthetized rodents and, given the complexity of central vagal brainstem neurocircuitry (see below), it is not unreasonable to assume that anesthetics may have differential effects on vagal efferent pathways. While studies have been carried out to measure gastric or intestinal motility in freely moving rats or mice (69, 444, 485, 521), none have addressed the specific question of balance between vagal efferent excitatory and inhibitory control of the GI tract.

DMV neurons also express the gene for paired-like homobox 2B (*Phox2b*), mutations of which may underlie dysautonomia (19, 141) as well as adenylate cyclase activating polypeptide 1 (*Adcyap1*) which may be involved in several aspects of neuroendocrine homeostasis and sickness behavior (199, 266). More recent studies that used genome wide expression profiles to classify DMV neurons identified seven genetically distinct subtypes of cholinergic DMV neurons as per expression of Grp, Pdyn, Gm4881, Atf3, Nppb, Trpv1, and Cck genes (445). Notably, *Pdyn*+ and *Cck*+ *DMV* neurons form completely distinct populations that are anatomically separate, with *Pdyn*+ neurons be located rostrally while *Cck*+ neurons being located caudally within the nucleus. Physiological studies previously suggested the potential for a physiological difference in function of the rostral vs the caudal DMV, with medial-rostral neurons inducing gastroexcitation (contraction) while rostral neurons induced gastroinhibition (relaxation) (102, 251, 384, 385). Support for this functional distinction was uncovered with findings that *Pdyn*+ and *Cck*+ DMV neurons appear to project to distinct postganglionic targets, with *Pdyn*+ axons selectively innervating nitrergic (inhibitory) enteric neurons and *Cck*+ axons selectively forming terminal arborizations around cholinergic (excitatory) enteric neurons. Additionally, *Pdyn*+ and *Cck*+ DM*V* neurons project to the glandular (corpus and antrum) stomach, but do not innervate either the or any other visceral organ studied (pancreas, gallbladder, lower GI tract), suggesting specific roles in mechanical digestion of ingested food, in line with their inferred anatomical location and target (445). Both *in vitro* and *in vivo* studies investigating DMV neurons and their efferent functions have suggested distinct neuronal populations may differentially control ongoing ‘tone’ or GI muscle tonic contractility vs phasic motility (53, 78, 188, 384) indicating the potential for further segregation of vagal efferent neurons according to their functional output.

In contrast, the vagal efferent influence on gastric parietal cells, hence gastric secretion, whether acid, pepsin, gastrin, or mucus appears exclusively excitatory or stimulatory, with

no reports of a direct vagal inhibition of secretion(407, 408). Perhaps most famously, Pavlov (1902) noted that the cephalic phase of gastric acid secretion is an entirely vagally mediated reflex (reviewed in: (247)) whereas both vagal and spinal pathways are involved in reflex gastric and intestinal mediated acid secretion in response to either distension of the stomach or stimulation of the mucosa (244). A significant body of literature supports the role of several central nuclei in the control of gastric acid secretion (see below: hypothalamus (lateral, ventromedial and paraventricular nuclei), the locus coeruleus (LC), the caudal medullary raphe nuclei and the amygdala) as befits their roles in digestion, homeostasis, and the physiological outcomes of emotional and behavioral regulation. Perhaps surprisingly, the ability of these central nuclei to modulate gastric secretion appears restricted to that of gastric acid, with only the medullary raphe nuclei having an apparent role in also stimulating gastric pepsin secretion in a vagally-dependent manner (494). Remarkably, while stimulation of the vagal brainstem induces acid secretion, it also induces release of prostaglandins, including PGE1, PGE2 and PGF2a, which act at the level of the gastric parietal cell to increase mucus production and inhibit acid secretion (26, 94), thus acting to protect the stomach from the potentially harmful effects of gastric acid.

Properties of vagal efferent motoneurons

Vagal efferent neurons are also non-uniform with respect to their intrinsic (morphological and biophysical membrane) properties, as well as their extrinsic synaptic inputs, which impacts their excitability, responsiveness, and functional efferent output (55). DMV neurons are spontaneously active pacemakers with both *in vivo* and *in vitro* studies noting an action potential firing frequency of approximately 1 pulse s^{-1} (301, 312, 369, 376, 461). Again – and importantly – these *in vivo* studies were carried out under anesthetized conditions and it is unclear the extent to which anesthesia impacts the excitability of DMV neurons. The voltage dependent ionic currents, I_H and I_{KIR}, which have been identified in the majority of DMV neurons (461) although it should be noted that the resting membrane potential of DMV neurons is within 1–2mV of action potential firing threshold, leading to responsive neurons whose firing frequency can be rapidly and easily increased or decreased with minor changes in neuronal excitability. Action potential firing rate is also modified by the differential expression and density of the transient outward potassium current, I_A, as well as calcium-dependent afterhyperpolarizing currents, most notably the apamin sensitive (SK) current (55). The involvement of charybdotoxin-sensitive (BK) afterhyperpolarization currents in DMV neurons is more controversial, with electrophysiological studies reporting their presence in the guinea-pig and rat (394) while other studies found only apamin-sensitive (SK) afterhyperpolarization (AHP) currents (55, 393). Of interest, however, was the finding that charybdotoxin-sensitive (BK) AHP currents were upregulated in DMV neurons following vagal nerve damage, either vagotomy or peripheral perivagal capsaicin exposure (52), suggesting that larger AHP currents appear in response to neuronal damage, potentially as a means of preventing over- or hyper-excitation. This also implies that intrinsic DMV membrane properties are not static, but can be modulated in response to physiological or pathophysiological challenge.

The amplitude and decay kinetics of the calcium-dependent (SK) AHP current also differ in functionally distinct types of DMV neurons; neurons that innervate the stomach and are

located within the medial DMV, for example, have a shorter and faster AHP (55). Coupled with a higher membrane input resistance and smaller cell volume, gastric-projecting neurons displayed a greater action potential firing rate in response to depolarizing current, hence are more likely to be responsive to synaptic inputs. In contrast, neurons that innervate the cecum and are located within the lateral DMV have a larger and longer AHP, a lower membrane input resistance, and larger cell volume; this results in a lower frequency of action potential firing in response to depolarizing current and, most likely, a lesser response to synaptic inputs (57). DMV neurons are also known to express at least three different types of calcium channels – an ω-conotoxin sensitive (hence N-type current) conductance that contributes approximately 40% of the total calcium current, a nifedipine sensitive (hence L-type current) conductance that contributes approximately 20% of the total current, with the remaining current being sensitive to a combination of cadmium and nickel, likely to be a high voltage activated conductance (392). Calcium influx through the ω-conotoxin sensitive N-type calcium channel appears most responsible activation of the action potential AHP (SK) currents, which have been proposed to be in close spatial proximity to the N-type calcium channels (392). It remains to be determined whether neurons that display differences in the size or duration of action potential AHP currents (e.g., gastric vs intestinal DMV neurons) are due to differences in the spatial localization of these ion channels.

Morphologically, DMV neurons appear relatively uniform although characteristics (e.g., cell size and soma volume, dendritic extent) may vary within a given range and cell location (or column) within the nucleus (55, 208, 251, 303). Medially-located gastric projecting DMV neurons, for example, are smaller than laterally-located cecum-projecting neurons which also displayed a large dendritic field (55, 517) The dendrites of DMV neurons are most often oriented in the horizontal plane as are the cell bodies themselves. Of note, morphological studies have shown that the dendrites of DMV neurons can project into the NTS and area postrema, and even to the extent of penetrating the ependymal layer of the 4th ventricle (134, 208). While ependymocytes are typically thought of as limiting contact with (hence signaling from) the cerebrospinal fluid (CSF), the dorsal vagal complex (i.e.,DMV, NTS and area postrema, AP; DVC) is a circumventricular organ, surrounded by fenestrated capillaries and a leaky blood brain barrier, hence has much greater access to circulating factors than many brain regions (99, 136). Furthermore, subependymal CSF-contacting neurons (CSF-cNs) have been identified within the DVC. These neurons have a transient receptor potential (TRP) channel phenotype, extend a neuronal process towards the central canal, and have been proposed to act as mechano-, chemo-and osmo-sensors, allowing integration of CSF signaling and autonomic homeostasis (342). Brainstem DMV neurons are certainly capable of responding directly to peripheral neurohormones; even after selective surgical removal of vagal afferent inputs to the brainstem, for example, NTS and DMV neurons were activated by peripheral administration of the GI neurohormone, cholecystokinin (CCK), implying a direct action or circulating factors at the level of the DVC (23).

Although their intrinsic biophysical properties endow them with the ability to fire action potential spontaneously, the activity and excitability of DMV neurons is modulated by synaptic inputs, principally from the adjacent NTS but also from other brainstem, midbrain, and cortical nuclei ((18, 151, 462) see also below). The NTS is the primary source of synaptic input to DMV neurons, however, providing excitatory glutamatergic, inhibitory

GABAergic and catecholaminergic (excitatory or inhibitory depending upon the receptor activated) inputs to the DMV (18, 151, 385, 462). Both *in vitro* and *in vivo* studies suggest that NTS GABAergic inputs play the most critical role in modulating DMV neuronal activity (142, 315, 418, 462) although, again, it must be borne in mind that *in vivo* recordings were conducted in anesthetized animals and the potential differential modulation of presynaptic neurons and synaptic inputs by anesthetics cannot be dismissed. While both ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors are present on DMV neurons (18, 59, 110, 418), in adult neurons GABA produces a neuronal inhibition under basal conditions, predominantly via activation of $GABA_A$ receptors because of the negative chloride equilibrium potential in these neurons. Interestingly, activation of synaptic (γ subunit containing) $GABA_A$ receptors does not appear to induce a prominent membrane hyperpolarization in DMV neurons (142) but rather appears to result in 'shunting inhibition' by reducing membrane resistance and inhibiting the ability of ongoing glutamatergic inputs to induce a membrane excitation. In contrast, activation of peri- and extra-synaptic (δ subunit containing) $GABA_A$ receptors contribute substantially to the tonic inhibition of DMV neurons (45, 143, 277). The density and location of $GABA_A$ receptors is not static, however; systemic hyperglycemia, for example, increases the expression of δ- and γ-subunit containing receptors at synaptic and peri/extrasyanptic sites within days as well as an increased contribution of δ-subunit containing GABA receptors to the tonic inhibitory current (45, 277).

Several groups have shown, using both in vivo and in vitro studies, that DMV neuronal excitability and vagal efferent regulation of the GI tract is modulated by a variety of neurotransmitters, neuromodulators, and neurohormones either acting directly to alter DMV membrane excitability, or indirectly to alter synaptic transmission onto DMV neurons. Curiously, although GABAergic input to DMV neurons exerts critical control over neuronal excitability (hence vagal efferent output), few neurotransmitters/modulators/hormones have been shown to modulate GABAergic synaptic transmission under basal physiological conditions. These same neurotransmitters/modulators/hormones are, however, able to modulate glutamatergic transmission which appears to exert little direct influence on vagal efferent control of the GI tract under basal conditions. This apparent disparity remained puzzling until a series of studies demonstrated that the 'state of activation' of cAMP-PKA signaling within GABAergic nerve terminals is low, preventing modulation of inhibitory transmission to DMV neurons (38, 53, 54, 58, 61, 64, 65). These low levels of cAMP-PKA activity within inhibitory NTS-DMV inputs appears related to the ongoing tonic activation of presynaptic group II metabotropic glutamate receptors (mGluRII; (188) by glutamate released from monosynaptic vagal afferent inputs (380). Blocking these presynaptic mGluR – either by removing vagal afferent inputs surgically, pharmacologically inhibiting group II mGluR, or activating adenylate cyclase directly – appears to induce trafficking of several receptors (to date: μ-opioid, 5-HT_{1A}, α adrenoceptors, oxytocin OT1, NPY Y1 and Y2 receptors) to the GABAergic synaptic terminals allowing their activation and hence the modulation of tonic GABAergic transmission (reviewed in (62, 63).

Inhibition of presynaptic GABAergic transmission appears to be a common means by which DMV neuronal activity, hence vagal efferent output to the GI tract, is regulated under a variety of homeostatic as well as pathophysiological conditions. Activation of presynaptic

5-HT receptors, for example, has little effect on vagally mediated gastric functions (311, 316); following exposure to thyrotropin releasing hormone (TRH), however, 5-HT activates presynaptic 5-HT_{1A} receptors, inhibits NTS-DMV GABAergic transmission resulting in the 'disinhibition' of DMV neurons (311, 316, 417, 509). Physiologically, this may explain the significant increase in gastric acid secretion that results from cold exposure stress which is known to activate TRH- and 5-HT-containing caudal raphe synaptic inputs to the DVC and augment gastric acid secretion (145) (316, 428). In a similar manner, descending oxytocin (OXT) inputs from the paraventricular nucleus of the hypothalamus (PVN) to the DVC are tonically active, yet do not modulate GABAergic transmission to DMV neurons. Following stress or exposure to the prototypical stress neuropeptide, corticotropin releasing hormone (CRF), however, the ability of OXT to inhibit GABAergic transmission is uncovered, DMV neurons are disinhibited, and vagal efferent outflow to the GI tract counteracts the gastric effects of stress (53, 188). As a final example, GI neurohormones such as CCK that are released in response to meal ingestion also uncover the ability of inhibitory NTS-DMV GABAergic transmission to be modulated (60) which allows the 'gain' of vagal efferent output to the GI tract to be altered in alignment with homeostatic demand.

While the majority of work to date has focused on modulation of GABAergic signaling to DMV neurons, recent studies have also uncovered glutamatergic neuroplasticity within the same neurocircuits. Specifically, while the majority of glutamatergic signaling occurs via activation of AMPA receptors, uncovering the activation of NMDA receptors appears to have a prominent role in modulating and maintaining glutamatergic signaling within vagal neurocircuits (90), as shown previously for upstream vagal afferent-NTS synapses (519). Specifically, the regulation of caloric intake in response to acute high fat diet (HFD) exposure involves the activation of synaptic NMDA receptors (NMDAs) in DMV neurons. Briefly, upon initial exposure to a palatable, calorically dense HFD, rodents become hyperphagic. Within 3–5 days, however, rodents decrease the amount of food HFD ingested to restore caloric balance and this recovery of homeostatic control appears due to activated brainstem astrocytes releasing gliotransmitters (glutamate and ATP) which permits the activation of extrasynaptic NMDA receptors first, and then subsequently the activation of synaptic NMDA receptors. Ultimately, this causes dysregulation of vagal efferent control of the stomach resulting in a delay in gastric emptying and a reduction in food intake (91–93). Clearly, astrocytes activity and reactivity is modulated by a variety of different mechanisms and processes(90, 125, 349); it remains to be seen whether this is a common means by which vagal neurocircuits – including those controlling food intake – are modulated under physiological as well as pathophysiological conditions. Nevertheless, it is clear that neuroplasticity within vagal brainstem neurocircuits is more common than previously assumed and that vagal control of GI functions will be the result of neuronal and synaptic integration at multiple levels.

Parasympathetic innervation and control of the colon

The efferent vagus provides innervation to the proximal colon (and transverse colon in humans); the extent to which the vagus may innervate the terminal colon has been debated throughout the history of autonomic neuroscience. Langley (260) described the majority of innervation to the distal or descending colon as arising from preganglionic neurons

within the intermediolateral column (IML) of the lumbosacral spinal cord (S1-S4; Figure 5). Other studies, both nerve tracing (as well as physiological have), however, described a functional role for vagal innervation to the distal colon (5, 33, 109) (261). As described for cranial preganglionic parasympathetic neurons, the lumbosacral parasympathetic neurons are cholinergic although the identification of enkephalin and nitric oxide containing neurons raised questions as to the ontogeny of these neurons (70, 155, 227). Indeed, Espinosa-Medina et al (126) proposed that, based on genetic, neurochemical, and anatomical phenotypes, sacral preganglionic neurons may be better characterized as "sympathetic" rather than "parasympathetic". Notably, their findings that sacral preganglionic neurons (i) express nitric oxide synthase early during development similar to thoracic (sympathetic) but not cranial (DMV) preganglionic neurons, (ii) display a transcription factor phenotype similar to thoracic preganglionic neurons (*Foxp1*) but not cranial preganglionic neurons (*Phox2b* and *Tbx20*), and (iii) follow a developmental migration pattern distinct from cranial preganglionic neurons (independent of $Sox10^{+}$/Phox2b Schwann cell precursors), prompted the re-classification of these preganglionic neurons as "sympathetic". This was, and is, controversial given that it appears to contradict a century of accepted autonomic anatomy and physiology, and has been challenged by others noting the early embryonic timepoint at which transcription factors were assessed (E13.5), potential differences in the temporal patterning of transdifferentiation of sympathetic vs parasympathetic preganglionic neurons (notably cranial nerves may express tyrosine hydroxylase without every synthesizing norepinephrine (258, 263), while DMV neurons have been shown previously to express nitric oxide synthase (251, 275) and the complex and variable nature of pelvic autonomic anatomy (190, 207, 332). From a functional physiological perspective, for example, stimulation of the pelvic splanchnic nerve (sacral parasympathetic) and hypogastric (sympathetic) nerves have different effects of erectile tissue, supporting the concept of dual innervation. The most conservative outlook would be to emphasize that sacral autonomic outflow arises from the spinal cord and that pelvic autonomic innervation may be "mixed" or, at the very least, less clear cut that autonomic innervation of other visceral organs.

Irrespective of their ontogeny, phenotype or anatomic label, stimulation of sacral preganglionic neurons project to GI target organs either directly, via innervation of myenteric ganglia within the colon, or indirectly, via innervation of postganglionic neurons within the pelvic (hypogastric) plexus, with postganglionic pelvic ganglion neurons then innervating myenteric ganglia of the colon and rectum via the rectal nerves (146, 260). As with cranial preganglionic parasympathetic outflow, there appears to be a dual excitatory (cholinergic and atropine sensitive) and inhibitory (NANC, nitric oxide and/or purine mediated) innervation of the colon (129). The role of extrinsic parasympathetic innervation to the distal or descending colon appears far less integrative and modulatory than the upper GI tract which has more complex motility patterns. The distal colon displays relatively simpler (or, at least, less complex) motility patterns and peristaltic reflexes designed to transport fecal contents distally. Extrinsic parasympathetic innervation to the colon regulates propulsive motility prior to defecation and damage to these nerves is often associated with dysmotility and constipation. Notably, colonic motility patterns can display some degree or recovery of function following extrinsic denervation suggesting the role of the extrinsic

parasympathetic innervation is integrative and modulatory, rather and not necessarily critical to the initiation or continuation of colonic motility (317, 331).

Highlights

- The NTS and AP receive vagal afferent inputs from thoracic and subdiaphragmatic organs. The NTS also receives sympathetic afferent inputs via the spino-solitary tract. As the only area that receives both direct vagal and sympathetic afferent information, the NTS is an important integrator of visceral sensory information.
- The DVC (i.e, NTS, DMV, and AP) is a circumventricular organ and its fenestrated capillaries and leaky blood brain barrier allow greater access to circulating factors.
- The NTS has reciprocal connections with many other brainstem, midbrain, and cortical nuclei allow it to integrate ascending interoceptive information with descending modulatory inputs.
- The NTS sends glutamatergic, catecholaminergic, and predominantly GABAergic synaptic inputs to the adjacent DMV, which contains the preganglionic parasympathetic cholinergic motoneurons that relay the integrated output signal to visceral organs, including the GI tract, via the efferent vagus nerve.
- DMV neurons form two pathways to regulate gastric functions; an excitatory pathway, activation of which induces contraction via activation of postganglionic cholinergic neurons and activation of smooth muscle muscarinic receptors, and an inhibitory pathway, activation of which induces relaxation via activation of postganglionic NANC neurons and release of predominantly NO and VIP.
- DMV neuron excitability, hence vagal efferent output, can be altered via intrinsic changes (e.g., high fat diet and diet induced obesity decreases DMV excitability via intrinsic alterations in membrane biophysical properties (35)), or via modulation of synaptic inputs in response to, for example, acute high fat diet (91–93), stress (78, 211, 212), or vagal afferent signaling (188).

Sympathetic innervation and control of the gastrointestinal tract

Sympathetic innervation to the GI is provided by preganglionic neurons contained within the IML of the thoracic (T6-T9 – stomach) and lumbar (L2-L5 – colon) levels although, in the human, some input may be provided by neurons contained within the caudal thoracic segment. As preganglionic neurons, they are *a priori* cholinergic, although neuropeptide neurotransmitters may also exert some presynaptic effects to modulate cholinergic transmission. Most postganglionic sympathetic neurons are contained within distinct ganglia located either within the paravertebral sympathetic chain or in discrete prevertebral ganglia, which themselves offer the opportunity for neuronal integration via

convergence of inputs and neuronal pacemaking activity (128, 306, 317). The stomach is innervated by postganglionic sympathetic neurons located within the celiac ganglion, the small intestine by neurons within the superior mesenteric ganglion, and the colon by neurons within the inferior mesenteric or pelvic ganglia. As noted above, pelvic ganglia also contain cell bodies of parasympathetic postganglionic neurons (hence stimulation of postganglionic nerve bundles will activate both sympathetic and parasympathetic responses). In fact, the co-localization of these postganglionic neurons may allow neuronal cross-talk that underlies inter-organ communication – and potentially dysregulation and co-morbidities in pathological states. Norepinephrine is the principle neurotransmitter used by postganglionic sympathetic neurons, although roles for neuropeptides, including NPY, somatostatin, galanin, and purines, has been reported (206).

Activation of sympathetic innervation to the GI tract is predominantly inhibitory, decreasing motility via both pre- and post-synaptic effects to modulate enteric (both myenteric and submucosal) neuronal activity (338, 412, 442, 483). Direct innervation of GI smooth muscle, either longitudinal or circular, is relatively sparse although it should be noted that innervation to sphincter muscle is dense and sympathetic activation results in sphincter contraction(285, 317). Sympathetic neurons also target non-neuronal cells that modulate motility patterns, including ICC and glia as well as non-neuronal cells that regulate immune functions (glia, macrophages) as well as epithelial barrier functions(419). The GI tract has an extensive and dense vascular supply and, as a result, the neurovascular control exerted by postganglionic sympathetic neurons plays a significant role in the regulation of overall blood pressure. Importantly, sympathetic input to the GI tract appears to have non-uniform effects to modulate motility and contractile patterns. Stimulation of sympathetic input to the colon causes inhibition of peristaltic and propulsive motility but facilitates motility patterns in the proximal colon (331, 419). From an overall perspective, however, this appears consistent with a physiological and functional role to co-ordinate movement of ingested contents distally through the GI tract.

Unlike extrinsic parasympathetic input, however, sympathetic inputs to the GI tract do not appear to be tonically active, at least in terms of the regulation of contractile activity and motility. Cutting splanchnic nerves has long been recognized to result in a modest increase in peristalsis. In contrast, sympathetic innervation to vasomotor and secretomotor targets is tonically active; stimulating sympathetic nerves increases fluid absorption independently of changes to neurovascular tone, but cutting those same nerves increases secretion (160, 351) implying that secretion and absorption are regulated independently and may be modulated by changes in sympathetic tone in alignment with homeostatic needs or demands. Or note, vasomotor tone is regulated by descending (CNS) inputs independently of ongoing enteric activity in contrast to motor and secretomotor inputs that can be, and are, modulated by ongoing activity within the myenteric and submucosal plexuses as well as sensory afferent inputs (477, 478).

CNS regulation of sympathetic and parasympathetic control of gastrointestinal functions

The brainstem, including DMV and especially NTS, is highly integrated with other nuclei involved in autonomic homeostasis. The NTS in particular has reciprocal connections with several other central nuclei which presumably assists in integration of ascending (interoceptive) and descending (motor) homeostasis. Earlier dye tracing studies allowed the identification of other brainstem, midbrain, and cortical nuclei that project to hindbrain vagal neurocircuits, while transsynaptic virus tracing studies have allowed the identification of upstream polysynaptic pathways. As the only nucleus that receives *direct* input from both sympathetic (spinal) and parasympathetic (vagal) inputs, identification of discrete sympathetic vs parasympathetic upstream NTS pathways has been hampered, the although selective surgical nerve sections or deafferentations has increased the selectivity of these tracing techniques (77, 381). Newer genetic tracing studies have increased precision in pathway identification and specificity, particularly in precision by which collateral inputs and projections can be assessed. The following sections will outline the role of CNS areas (brainstem, midbrain, cortical) in the regulation of sympathetic and parasympathetic inputs to the GI tract, and their role in regulation of GI functions.

Brainstem nuclei regulating gastrointestinal functions

Area postrema

The area postrema, located immediately dorsal to the NTS, is a highly vascularized circumventricular organ that has been linked most prominently with chemoreception, including nausea and emesis as well as feeding and satiation, and the integration of cardiovascular reflexes and fluid homeostasis (391, 495, 514). Neurophysiological recordings have shown that area postrema neurons can be spontaneously active, most likely due to the expression of the hyperpolarization activated cation current, I_H (415). Afferent input to the area postrema arises from the glossopharyngeal and vagus nerves in addition to inputs from the carotid sinus and aortic depressor nerves (346, 359, 490), as well as descending inputs from the hypothalamus (193). Area postrema neurons display receptors for, and respond to, a variety of neurotransmitters/modulators/hormones, as well as inflammatory mediators (474). Surprisingly, given the array of potential substances that area postrema neurons can respond to, recent genetic approaches used single cell RNA sequencing identified a surprisingly small number of distinct neuronal phenotypes, of which three were GABAergic inhibitory neurons and four were glutamatergic excitatory neurons. The finding that receptors expressed by some neurons can engage multiple intracellular signaling pathways led to the suggestion that area postrema neurons may function by funneling an array of different types of stimuli into a common type of downstream signal for malaise or nausea (515). The dendritic projections of area postrema neurons intermingle with those of the NTS and DMV, allowing integration of homeostatic reflexes with circulating factors. Area postrema neurons themselves project most prominently to the NTS, with additional physiologically important projections to innervate the DMV, locus coeruleus, parabrachial nucleus (PBN) and nucleus ambiguus (NAmb), reflecting the prominent role of this nucleus in the regulation and co-ordination of vomiting (366).

Reticular formation and ventrolateral medulla

The reticular formation (substantia reticulata; so-called because of its net or mesh-like appearance) is a set of loosely interconnected nuclei that extends throughout the lower extent of the brainstem rostrally through the upper end of the midbrain. Although not directly modulating GI functions *per se* the reticular formation appears to be important in the integration of cardiovascular, respiratory, and GI reflexes. Distention of the stomach, for example, induces vagal sensory mediated reflex alterations in heart rate and blood pressure in several species (286, 339, 454, 468) that is associated with c-fos activation in the reticular formation (321). Meal ingestion requires an increase in blood flow in the superior mesenteric artery which, in turn, requires an increase in cardiac output and peripheral vasoconstriction to prevent a fall in systolic blood pressure. Stimulation of abdominal (GI) vagal afferents causes a reflex increase in blood pressure (100, 150, 333) while gastric distention causes an increase in muscle sympathetic nerve activity (the gastrovascular reflex; (386)) possibly due to a change in baroreflex sensitivity in response to gastric stretch.

As the primary recipient of vagal sensory inputs from thoracic and subdiaphragmatic organs (hence GI, taste, gustatory, cardiovascular, and respiratory information), the NTS plays a critical role in integrating and modulating homeostatic reflexes across organ systems. For example, both the caudal ventrolateral medulla (CVLM) and rostroventrolateral medulla (RVLM) receive dense excitatory synaptic inputs from the NTS. The RVLM then projects directly to sympathetic preganglionic neurons in the IML of the spinal cord to regulate vascular tone (167, 168). RVLM neurons in particular are activated by physiological (non-noxious) gastric distention (452, 453) as well as by intragastric administration of bitter tastants (173). In contrast, CCK released following meal ingestion induces a vagally-dependent inhibition of RVLM neurons that, in turn, decreases vascular tone in the splanchnic bed hence, increases post-prandial blood flow to the GI tract (403, 480) suggesting that activation of vagal afferents induces pathway-specific alterations in neurovascular responses hence blood pressure.

Caudal Medullary Raphe Nuclei

The raphe nuclei can be subdivided into two major groups based upon location within the CNS. The rostral raphe nuclei are located within the midbrain and rostral pons and innervate the amygdala, hippocampus, thalamus and basal ganglia as per their involvement in behavioral outcomes such as mood, stress, cognition, sleep-wake cycle, memory, sexual function, to name a few. The caudal raphe nuclei (or caudal medullary raphe nuclei comprised of the raphe magnus, obscurus, and pallidus), in contrast, are located within the caudal pons and medulla and innervate the DVC and spinal cord as per their involvement in regulation of nociception, motor responses, and autonomic functions including gastric and colonic activity (119, 192, 441).

Several studies have highlighted the role of the caudal medullary raphe nuclei in vagally-mediated regulation of gastric motility and acid secretion. Subpopulations of thyrotopin releasing hormone (TRH), serotonin (5-HT), and substance P (SubP) containing neurons in the raphe pallidus and obscurus innervate the DVC (191, 294, 347, 450, 451). Both microinjection of TRH into the DVC and stimulation of the raphe pallidus and/or obscurus

induce an increase in gastric motility and acid secretion, in a manner that is attenuated by application of a TRH antibody into the DVC (145, 182, 183, 428, 440, 505). TRH activates vagal efferent neurons within the DMV directly (463), as does 5-HT (57) and SubP (270). Notably, as described above, TRH 'uncovers' presynaptic actions of 5-HT at 5-HT_{1A} receptors to decrease the tonic GABAergic drive to DMV neurons, increasing vagal efferent outflow to the GI tract (61). Physiologically, caudal raphe neurons that innervate the DVC are associated with the vagally-dependent increase in gastric acid secretion in response to the sight, sound, smell, and taste of food – the cephalic phase of digestion as proposed by Pavlov (reviewed in (245, 246)) - as well as with the increase in gastric acid secretion and motility in response to cold stress (73, 145). The former reflex is prevented by intracisternal application of TRH receptor oligosense antibodies (304), while the latter is prevented by DVC application of TRH antibodies (183).

Serotonergic neurons within the medullary raphe nuclei have also been shown to innervate preganglionic neurons within the lumbosacral 'defecation center'. Both electrical stimulation as well as more precise chemogenetic stimulation of medullary raphe neurons that project specifically to the lumbosacral spinal cord increased colorectal motility but, interestingly, only under conditions when GABAergic transmission in the lumbosacral spinal cord was blocked (404). While the source of GABAergic transmission has not been elucidated completely, these results do raise the possibility that supraspinal areas involved in control of defecation exert both excitatory and inhibitory effects on colorectal motility (see Hypothalamus section below). Thus, the caudal medullary raphe nuclei appear to play significant roles in GI functions, both gastric and colonic, in response to both physiological and pathophysiological processes.

Highlights:

- The anatomical location of the area postrema (AP) allows it to be close contact with circulating factors including potential neurotoxins and infections or inflammatory agents. The connectivity of the AP with other nuclei involved in complex autonomic regulatory pathways including the NTS, DMV, PBN, and NAMb reflect its involvement in malaise, nausea, and vomiting reflexes.
- The reticular formation and VLM are involved in integrating GI, cardiovascular, and respiratory reflexes
- The caudal medullary raphe nuclei provide serotonergic (5-HT), TRH, and SubP innervation to the DVC, and are involved increasing gastric acid secretion in response to cold stress as well as the cephalic phase of digestion

Midbrain nuclei regulating gastrointestinal functions

Cerebellum & Vestibular System: Although most associated with its roles in motor control, the cerebellum also exerts effects on GI functions, most notably in response to motion sickness associated nausea and vomiting (95). Neuronal tracing studies showed that the cerebellum, particularly the fastigial and interpositus nuclei, innervate the NTS (27, 28, 340). The NTS also receives inputs from the vestibular system (21, 22, 74, 390). In addition

to direct inputs to the DVC, the cerebellum can also modulate GI functions by indirect projections via the vestibular nucleus, hypothalamus, parabrachial, and Kolliker-Fuse nuclei (20, 432) (Figure 6).

Physiological studies have further indicated that the NTS in particular receives convergent inputs from the cerebellar or vestibular systems and the GI tract (36, 430), although it should be noted that abdominal/GI vagal afferent input is not essential to induce emesis (259, 489). Both clinical (254) and preclinical (319) imaging studies have shown that the cerebellum responds to gastric distension, with activation increasing in parallel with distention volume or intensity. Stimulation of the cerebellum can induce either gastric excitation (activation of the vagal cholinergic efferent pathway and/or inhibition of the NANC inhibitory pathway) and gastric inhibition (increased sympathetic efferent activity as well as increased adrenal release of catecholamines) (276, 296), suggesting that the GI outcomes in response to gastric stimulation may be dependent upon the balance of parasympathetic vs sympathetic outflow. Clearly, the cerebellum plays a significant role in integrating somatic motor and visceral reflexes, while its ability to regulate and modulate several autonomic (cardiovascular, respiratory) and behavioral (emotional and cognitive (reviewed by (365, 523) responses suggests a more wide-spread integrative capability.

Parabrachial Complex: The parabrachial nucleus (PBN) is a composed of a group of nuclei in the dorsal pons that is composed of at least 13 different subnuclei or regions, but can be broadly separated into the medial and lateral subdivisions which, together with the Kolliker-Fuse nucleus, also known as the subparabrachial nucleus located within the ventrolateral extent of the nucleus, comprise the parabrachial complex (PB Complex). The medial PBN is involved in taste and receives inputs from the rostral NTS while the lateral PBN, in contrast, is involved in visceral sensation, and receives inputs from both the NTS and area postrema (169, 335). While each subnucleus or region of the PBN is associated with a distinct pattern of inputs and projections, the organizational plan of the PB complex appears more aligned with the type of information it receives and the neurochemical phenotype of inputs/outputs, suggesting another form of ‘labeled lines’ with respect to autonomic neurocircuits (320, 329, 352).

The medial PBN sends descending projections via the ventrolateral medullary pathway to the rhinal fissure, the N.Amb and both A5 (superior olivary complex in the pons) and A1 (ventrolateral medulla) noradrenergic cell groups, while the lateral PBN sends descending projections to the NTS, and both A5 and A1 noradrenergic groups. In terms of ascending projections, both medial and lateral PBN innervate similar areas; dorsal raphe nuclei, the thalamus and hypothalamus and zona incerta (with more extensive projections from the lateral PBN), the bed nucleus of the stria terminalis (BNST), the amgydala, and the substantia innominata, with the medial PBN having additional projections to cortical areas (insular cortex, frontal cortex, and infralimbic cortex (401)(Figure 6). The extent of inputs to, and projections from, the PB complex denotes its importance as a relay between ascending medullary autonomic reflexes and descending forebrain cognitive and behavior centers, and provides a means by which visceral (GI) sensory information can be integrated with affective and emotional responses. Most studies investigating the physiological function of the PB complex have focused on its neurocircuitry and neuronal activation in feeding,

taste, and nausea (329), although neurons within the PB complex also respond to gastric distention (224). Studies involving PB complex stimulation concentrated on a variety of cardiovascular or respiratory outcomes, with little apparent effect on GI functions although, notably, one study in which CRF was microinjected into the PB complex observed no effect on colonic transit (323).

Barrington's Nucleus: Barrington's Nucleus – also commonly known as the pontine micturition center – is located medial to the locus coeruleus (LC) within the rostral pons and is involved in supraspinal regulation of both colon and bladder function via projections to preganglionic parasympathetic neurons of the lumbosacral spinal cord. Transsynaptic retrograde tracing studies demonstrated that, in addition to populations of neurons within Barrington's Nucleus that innervate preganglionic neurons projecting to either the colon or the bladder, a discrete a population of Barrington's Nucleus neurons projects to preganglionic neurons innervating both organs (388, 389). Functional studies support this anatomical evidence; most Barrington's Nucleus neurons increase their activity in response to bladder distention, with approximately half of those neurons also responding to colonic distension (389). Similarly, as per its role in micturition, stimulation of Barrington's Nucleus increases bladder contraction, but also increases colonic contractile activity (353) suggesting a common convergent pathway for regulation of bladder and colon.

The majority of Barrington's Nucleus (Barr) neurons are CRF-immunoreactive ($Barr^{CRF}$), and trans-synaptically labeled neurons projecting to the colon have also been shown to be CRF containing (469, 470) as are the majority of neurons responsive to colon distention (389). This may be species dependent, however, as studies in *suncus murinus* have shown that CRF-containing neurons were not present in the region of the pons assumed to be Barrington's Nucleus in this species (431). Despite their prominent spinal projections, there is little direct evidence that the $Barr^{CRF}$ neurons in the mouse and rat release CRF at the level of the spinal cord, however. Several studies noted the presence of glutamatergic Barrington's nucleus neurons ($Barr^{Vglut2}$) in addition to co-localization of glutamate in CRF neurons and optogenetic stimulation of Bar^{CRF} neurons induces glutamatergic responses in preganglionic neurons in the sacral spinal cord (226) while optogenetic stimulation of $Barr^{Vglut2}$ neurons alone is sufficient to induce bladder contractile activity (482).

Many $Barr^{CRF}$ neurons also have extensive collateral projections to the adjacent locus coeruleus (LC; which was not itself labeled by transsynaptic virus application to the colon (388) Figure 6), and lesions of Barrington's Nucleus reduced LC activation in response to colonic distension (387). Given the role of the LC in the modulation of forebrain activity, this suggests a means by which pelvic visceral functions (including colonic activity) can be integrated and co-ordinated with cognitive, behavioral, and affective responses, including in the GI responses to stress and anxiety (117, 438), indeed CRF levels increase in Barrington's Nucleus in response to acute and chronic stress (200, 201). $Barr^{CRF}$ neurons also project to the lateral DMV (Figure 6), the area containing preganglionic vagal motoneurons that innervate the proximal colon via the celiac and accessory celiac efferent vagal branches (470). This may also be a means by which colon responsive $Barr^{CRF}$ neurons can also influence more proximal GI activity. Or interest, although most studies have focused on the role of Barrington's Nucleus to modulate parasympathetic outflow to the colon, tracing

studies have also shown innervation of preganglionic neurons within the thoracic spinal cord, hence the potential not only for modulation of sympathetic outflow (75), but the integration of both sympathetic and parasympathetic control of the GI tract.

In addition to receiving inputs from the colon and bladder related visceral afferents, $Barr^{CRF}$ neurons also receives projections from the periaqueductal gray (PAG) and the lateral hypothalamus (LH), with additional inputs arising from the medial preoptic nucleus (MPO), NTS, PB complex, raphe nuclei, zona incerta, tubero- and pre-mammillary nuclei, bed nucleus of the stria terminalis (BNST), hypothalamus (dorsal, ventromedial, and paraventricular), as well as cortex (infralimbic and insular areas)(469). Also notable is the finding that $Barr^{CRF}$ neurons have surprisingly long dendritic projections that may extend well outside the boundaries of the nucleus itself in rostral (extending along the ventral aspect of the lateral dorsal tegmentum and pedunculopontine tegmental nucleus), dorsal (extending towards and along the 4^{th} ventricle), and caudal (extending towards, and overlapping with, dendrites from, the LC) directions (482). Thus, the input and output connection to and from Barrington's Nucleus suggest an integrative role within a range of autonomic functions, including the assimilation of central and peripheral responses to colonic sensory inputs.

Periaqueductal gray: The periaqueductal gray (PAG) within the midbrain surrounds the cerebral aqueduct from the dorsal tegmental nucleus to the most rostral level of the oculomotor nucleus at the level of the posterior commissure, and is organized into longitudinal tracts that connect the forebrain with autonomic brainstem centers. In addition to its effects on autonomic outcomes, the PAG receives ascending pain and temperature information via the spinothalamic and spinomesencephalic tracts, and is the primary center by which descending pain modulation occurs (reviewed in (516)).

NTS catecholaminergic (TH)-immunoreactive neurons provide dense innervation to the PAG, as do neurons within the rostroventrolateral reticular nucleus (RVL; involved in the integration of cardiovascular and respiratory reflexes). The PAG additionally receives inputs from spinal cord neurons contained within laminae I and V (181, 228, 253, 437), hence receives convergent parasympathetic and sympathetic afferent information, including from the GI tract. Together with descending inputs from the hypothalamus and cortex (prefrontal, cingulate and both pre- and infralimbic areas; Figure 6), this allows the PAG to play a significant role in the integration of autonomic signaling with affective/emotional as well as cognitive information. The PAG sends projections to many of the areas it receives inputs from, including the amygdala, hypothalamus and spinal cord as well as brainstem nuclei including the dorsal raphe, LC, PB complex, and ventrolateral medulla (124, 127, 250, 272, 374, 382, 383). Ascending projections to the hypothalamus may be a means by which autonomic outputs, both sympathetic and parasympathetic, can be modulated, while descending projections to the PB complex may be a means by which ascending inputs, including visceral afferent as well as nociceptive signaling, can be 'gated' of modulated depending on behavioral state.

PAG neurons express c-fos, hence are activated, in response to noxious stimulation of the stomach (intragastric infusion of formalin (85)), proximal colon (distention (305)) and colorectal (distention (458)) regions. Of note, the 5-HT-containing neurons that were

activated by intragastric infusion of formalin were in the same ventrolateral PAG region as neuron activated by noxious somatic stimulation (subcutaneous injection of formalin into the forepaw) suggesting that visceral and somatic nociceptive pathways may converge or overlap at a supraspinal level within the PAG. Similarly, PAG neurons activated by nociceptive GI stimulation project to the hypothalamus (PVN) again suggesting an additional degree of integration and overlap of somatic and autonomic processing (120). The PAG may also be play a role in the integration of stress responses and GI outcomes; the water avoidance stress model, thought to involve both physical and psychological stress, activates the PAG and induces gastric mucosal damage in a manner likely dependent upon astrocyte activation and the ERK1/2 signaling pathway(144, 501).

As discussed above, nociceptive signaling is predominantly considered to be relayed centrally via spinal afferent pathways. Involvement of vagal afferents in nociception is less well defined although vagal afferents can be activated by, for example, esophageal, gastric or colonic distention into the nociceptive range (222, 223, 242, 256, 257, 487). In this regard, in a rodent model of DGBI, specifically induction of gastric hypersensitivity via temporary neonatal gastric irritation, vagotomy partially attenuated the pain responses to gastric distension, in a manner potentially involving the PAG (98). Imaging studies in humans have uncovered abnormal network connectivity in patients with DGBI (increased connectivity with the insular but decreased connectivity with orbitofrontal, dorsolateral prefrontal cortices as well as the hippocampus) and patients with high degrees of anxiety and depression had altered connectivity with the anterior cingulate cortex, precuneus, dorsolateral prefrontal cortex, and caudate (279). As discussed below, this suggests that patients with DGBI may have altered activity within the default mode network (DFN) in a manner that may also involve the PAG and pain processing (see below).

Activation of the PAG is well known to be involved in descending pain inhibition and induction of analgesia likely via inhibition of nociceptive neurons within the dorsal horn (516). Innervation of the spinal cord from the PAG is relatively sparse, however, suggesting that the resulting analgesia may be indirect in nature, possibly via projections to the dorsal raphe nucleus. The nucleus raphe magnus in particular has been implicated in these anti-nociceptive effects of PAG stimulation (2, 374) although it is unlikely to be the only pathway involved (147, 399).

Locus coeruleus: Located within the rostral pons adjacent to the lateral 4th ventricle, the locus coeruleus (LC; A6 noradrenergic nucleus) is the principle source of norepinephrine innervation to the CNS. Neurophysiological recordings, both *in vitro* (slice preparations; (497, 499)) and *in vivo* (juxtacellular recordings; (524)) have demonstrated that LC neurons exhibit spontaneous action potential firing, the rate of which is increased by sensory, autonomic, and nociceptive inputs. In contrast, the rate of action potential firing is decreased by sleep, leading to the proposed role of the LC in attention and arousal (reviewed in (297)). Neuroanatomical tracing studies have identified extensive inputs and projections to and from the LC (Figure 6; reviewed in (492)) including from NTS (see above; (473)), the hypothalamus (see below; (378)), Barrington's Nucleus (see above; (387, 433)), the PB complex (see above;(293)), and the PAG (see above; (293)). Descending inputs from the BNST, central nucleus of the amygdala (CeA) and prefrontal cortex

also allow integration of these autonomic inputs with forebrain information related to cognitive and affective/emotional behaviors (15, 293, 471). Although the LC appears well positioned to integrate both spinal and vagal GI sensory inputs with those from other nuclei involved in autonomic homeostasis, viral tracing strategies have determined that inputs to the LC are non-overlapping and topographically organized (492) which may be expected to decrease cross-system integration. As with Barrington's Nucleus neurons (see above), however, LC neurons have extensive dendritic arbors, with many inputs making monosynaptic connections onto these dendrites, potentially regulating LC activity and output (492)Travagli, 1996 #105}.

Efferent projections from the LC are equally extensive, including to areas involved in autonomic GI functions such as the brainstem (NTS; (104, 288, 492) and hypothalamus (PVN) (405)), and spinal cord (492, 493). Notably, differences have been identified in spinal cord innervation patterns with some studies noting extensive LC projections throughout the spinal cord while other studies did not find inputs to the thoracic spinal cord (hence unlikely to influence activity in the upper GI tract (96, 97, 225). Efferent projections to the brainstem are less well defined, however, although LC inputs to the DMV and N.Amb have been identified in the monkey (493). The LC also projects to the cerebellum, amygdala, thalamus, and cortex as might be expected given its role in influencing arousal and behavioral states. By 'gating' sensory inputs and increasing the signal to noise ratio, the LC is able to focus and 'tune' responses to specific stimuli (16, 360).

Immunohistochemical and physiological studies have demonstrated that LC neurons respond to GI sensory information, including gastric and colonic distention (123, 305, 387). Responses to colonic stimulation in particular appear to depend on CRF inputs, most $Barr^{CRF}$ neurons (387, 472) but also potentially from the hypothalamus, amygdala, and BNST (378). Stress increases CRF levels within both Barrington's Nucleus and the LC, and repeated stress sensitizes LC neurons to CRF which may play a role in the well-described GI outcomes of stress (105, 438, 439, 471). Certainly, microinjection of CRF into the LC increases both tonic and phasic colonic motility and transit and increases the water content of fecal pellets. In contrast, microinjection of CRF into the LC had no effect on upper GI (gastric) motility or emptying, but did decrease gastric acid secretion. Since this was unaffected by vagotomy, this was most likely to due to modulation of spinal sympathetic pathways (438).

The LC has additional well-defined roles in opioid related substance used disorders, with particular involvement in the physiological responses to dependence and withdrawal. LC neuronal activity is inhibited by acute opioid exposure (decrease in adenylate cyclase and/or increase in potassium conductance (460, 498). Chronic exposure to opioids, however, and the development of tolerance and dependence increases LC neuronal activity (upregulation of adenylate cyclase-cAMP signaling pathway. Independent of the prominent effects directly on the GI tract to modulate motility and transit, therefore, opioid peptides may also alter GI functions via actions centrally through actions to alter LC activity and downstream sympathetic and/or parasympathetic outflow.

Substantia Nigra: The substantia nigra, located within the midbrain, comprises two subnuclei, the pars compacta (SNpc; A9 catecholaminergic nucleus) and the more lateral pars reticulata. Widely recognized for its involvement in the regulation of fine motor functions, the presence of calcium and hyperpolarization-activated cationic channels in SNpc dopaminergic neurons allows them to exhibit a spontaneous pacemaker activity at 2–4 pulses sec^{-1} (265). While stimulation of the these dopaminergic SNpc neurons does not induce movement per se, the degeneration of their projections to the dorsal striatum induces the cardinal symptoms of Parkinson's disease (PD), i.e. rigidity, bradykinesia, and resting tremor (135, 314). There are, however, several extra-pyramidal symptoms associated with PD, including prodromal GI disturbances, such as esophageal dysfunctions, delayed gastric emptying, and severe constipation (reviewed in (373, 459).

The occurrence of GI symptoms in otherwise healthy people has been associated with an increased PD risk, and several lines of evidence indicate the role of ingested environmental \eurotoxin as a triggering factor in the etiology of PD (217, 273, 459). Indeed, the prodromal presence of synucleinopathy in the ENS and in the preganglionic neurons of the DMV prompted Braak and colleagues to put forward the hypothesis that, in many instances, idiopathic PD begins with the uptake of pathogens by myenteric neurons in which the presence of misfolded, pathological α-synuclein is observed (46, 47). The spread of the synucleinopathy to the CNS occurs via retrograde transport by the vagus nerve to the DMV and to higher CNS centers in a prion-like fashion(156, 429; Figure 7). This potential route of synucleinopathy transmission has been confirmed by a series of recent discoveries in which the existence of an anatomically defined, and physiologically functional, mono-synaptic pathway connecting the SNpc to vagal brainstem nuclei has been described (12, 503) (Figure 4). This nigro-vagal pathway appears to target selective subpopulations of DMV neurons; while microinjections of dopamine in the DMV induce gastroinhibition via interaction with dopamine 2 (DA2)-like receptors, in contrast, chemical or optogenetic activation of SNpc neurons activates DMV DA1-like receptors selectively to ultimately increase tone and motility of both the stomach and the proximal colon (44, 503). This nigro-vagal pathway may, therefore, play a central role in the etiology and the extrapyramidal issues observed in PD, and reinforces the pivotal position of the vagus nerve as a brain-gut (or gut-brain) conduit. Indeed, a large longitudinal study of patients that received truncal subdiaphragmatic vagotomy showed a considerable reduction in the incidence of PD (434), substantiated by the observation that electromyogastrography of patients in the acute post-vagotomy phase is remarkably similar to that recorded in PD patients (221). Using either well established Parkinsonian models (either intraperitoneal administration of large doses of paraquat or 6-OHDA administration in the SNpc) or a recently developed environmental model (oral administration of subthreshold doses of paraquat and lectin), this nigro-vagal pathway is compromised, and the occurrence of parkinsonism is prevented by subdiaphragmatic vagotomy (11, 12). It appears, therefore, that the anatomical connection between SNpc and DMV may serve both as a direct means by which environmental toxin are transported from the GI tract to the CNS ("bottom-up" model of pathology) as well as providing a potential explanation of the intriguing observation of pathological GI alterations observed following SNpc degeneration ("top down" model of pathology).

Highlights:

- The cerebellum responds to gastric distention and its stimulation can induce either gastric contraction or relaxation via both inputs to the DVC as well as indirect inputs via the hypothalamus, vestibular nucleus, hypothalamus, and PBN. It regulates and modulates several autonomic and behavioral responses and is particularly involved in gastric response to motion sickness and malaise.
- The parabrachial nucleus (PBN) plays prominent role in relay ascending interoceptive information as well as descending forebrain inputs and is involved in GI responses to emotional and affective stimuli.
- Barrington's Nucleus is involved in colon and bladder function, particularly in the integration of colon sensory inputs
- The PAG integrates ascending interoceptive inputs with descending forebrain inputs to modulate emotional and affective responses as well as integrating stress outcomes and gating nociceptive signals with behavioral state
- LC has non-overlapping inputs from the NTS and spinal afferents but the large dendritic field of these neurons allows integration between multiple autonomic systems. The LC responds to gastric and colonic sensory inputs and may modulate gastric secretion, mostly likely via spinal efferent pathways
- The SNpc regulates GI motility via direct monosynaptic projections to the DVC. This interconnectivity may be involved in the ascending spread of misfolded proteins such as a-synuclein, and provides an anatomical and functional basis for GI disorders in neurodegenerative diseases including Parkinson's Disease

Forebrain nuclei regulating gastrointestinal functions

Hypothalamus: As part of the diencephalon, the hypothalamus is part of the anterior forebrain, located at the floor of the third ventricle and just ventral to the thalamus. It is comprised of several distinct subnuclei that play various critical roles in autonomic homeostasis, including integrating neural and endocrine functions via the pituitary gland. Of all hypothalamic subnuclei, the paraventricular nucleus (PVN or PVH) and arcuate nucleus (ARC) are, perhaps, the most important in terms of integrating and regulating GI functions.

The PVN itself is a miniaturized autonomic homeostatic control center, that can be further subdivided into different distinct cell types and regions. It receives inputs from multiple areas involved in the integration of visceral inputs, including ascending projections from the spinal cord, NTS, and PB complex as well as descending projections from nuclei involved in the emotional and affective responses to those visceral inputs, including the BNST and amygdala (436). In general, the PVN can be subdivided into magnocellular and parvocellular divisions. Magnocellular neurons contain oxytocin (OXT) or arginine-

vasopressin (AVP), which can be released into the posterior pituitary and circulation where it has multiple functions. OXT can also be released centrally, either from axon terminals or dendritically where it can diffuse to exert actions over periods ranging from seconds to hours (486). Parvocellular neurons contain a variety of neuromodulators/hormones, including CRF, which can be released from axon terminals into the hypophyseal portal system of the median eminence where has critical roles in the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the co-ordination of autonomic stress responses. Parvocellular neurons also have descending projections to the PAG, PB complex, DVC, ventrolateral medulla and spinal cord sympathetic preganglionic neurons through which they exert multiple effects on autonomic functions (292, 402, 436). With regard to the regulation or modulation of GI functions, however, parvocellular CRF and OXT neurons projections to the brainstem have been shown to modulate NTS and DMV neuronal and synaptic activity (3, 121, 122, 188, 369), with several studies showing important roles for descending PVN^{CRF} and PVN^{OXT} neurons in the regulation of GI responses to stress (53, 211–213, 322). Both *in vivo* and *in vitro* studies have demonstrated that CRF induces a vagally-dependent gastroinhibition, via both direct and indirect (modulation of glutamatergic synaptic inputs) regulation of DMV neuronal activity, resulting in a decrease in gastric motility and tone via activation of the efferent inhibitory NANC pathway (53, 185, 269, 322). Furthermore, acute stress induces a gastroinhibition and a vagally-dependent delay in gastric emptying that is dependent upon brainstem actions of CRF (328). In contrast, central CRF leads to an acceleration of colonic motility and transit (439, 521) in a manner dependent upon activation of vagal and sympathetic pathways innervating the proximal and distal colon (202, 465). Stress also activates CRF containing neurons within both Barrington's Nucleus and the PVN, including those that innervate the locus coeruleus ((261, 387, 389); see above) which are involved in increasing colonic transit, effects which appear independent of the neurocircuits involved in stress-induced gastroinhibition (322), but which may also be important in increased arousal and anxiety-like responses and behaviors observed under these conditions.

In contrast, parvocellular PVN^{OXT} projections are important in anxiolytic or anti-stress responses. The PVN is the sole source of OXT inputs into the DVC, and OXT exerts a variety of effects – physiological and pathophysiological – to modulate GI functions (284, 486; Figure 8). Electrophysiological studies have shown that OXT can excite DMV neurons both directly (activation of a cAMP dependent but PKA independent inward current as well as activation of a PLCb- and cAMP-independent inward current as well as facilitation of presynaptic glutamate release (3, 121, 122, 188, 357, 369). Intracerebroventricular application of an OXT antagonist was shown to induce a gastroexcitation, implying that descending PVN^{OXT} projections exert a tonic effect to dampen gastric functions (131). These tonic OXT-mediated effects can be upregulated, however, and activation of PVN^{OXT} inputs following meal ingestion increases gastric motility and acid secretion in a vagally-dependent manner(282).

Oxytocin also plays an important role in the recovery of GI functions in response to stress. As noted previously, OXT has no effect to modulate tonic inhibitory GABAergic NTS-DMV neurons under basal conditions. Following exposure to CRF (53) or stress (212), however, OXT acts presynaptically to decrease GABAergic transmission, thereby disinhibiting vagal efferent outflow. In fact, following exposure to CRF or acute stress, the gastroinhibition

induced in response to brainstem application of OXT was reduced or reversed such that an increase in gastric tone was observed (53, 212). Thus, exposure to stress – and the release of CRF – also uncovers a mechanism by which those deleterious stress-induced effects of GI functions can be attenuated, namely increased release of OXT. Descending PVN^{OXT} projections are also critically important in the adaptation to stress, or the development of stress resilience.

In rodents, stress adaptation is associated with upregulation of these descending PVN^{OXT} projections, and recovery of appropriate vagally-dependent gastric functions, including gastric emptying (211–213). This suggests that hypothalamic-brainstem neurocircuitry is remarkably plastic and modulation of these descending inputs may be a means by which adverse stress-induced effects on GI functions can be mitigated or overcome.

The periventricular hypothalamus, particularly the posterior and intermediate areas, have also been shown to have a role in regulation of colonic/colorectal motility and defecation. In particular, although described as part of the descending pain inhibitory pathway, dopaminergic cells of the A11 region that projected to the lumbosacral spinal cord also increase colorectal motility. Furthermore, the increase in colorectal motility in response to noxious colonic stimulation as well as water avoidance stress was blocked following chemogenetic inhibition of A11-lumbosacral projection neurons (404). The involvement of this area in both pain and stress-induced colorectal function and defecation reflexes may be a means by which stress can exacerbate painful GI disorders such as, for example, irritable bowel syndrome (IBS).

The arcuate nucleus (ARC) of the hypothalamus, located adjacent to the median eminence and pituitary gland is also a circumventricular organ (99, 136) and ARC neurons can modulate their activity in response to a variety of circulating and humoral factors, several of which are also involved in GI functions (39). The ARC receives extensive inputs from several other brain regions involved in general autonomic regulation, including the NTS, PVN, BNST, and LC while also sending projections to brainstem and cortical regions involved in autonomic integration (DVC, PAG, limbic system, thalamus) highlighting the role of this nucleus - and the hypothalamus in general - in the integration of visceral, somatic and behavioral responses of GI functions, particularly in the regulation of food intake and energy homeostasis (421). In addition to its role in energy balance, the ARC has additional effects to modulate GI motility more directly. Almost two-thirds of ARC neurons respond to gastric distention (excitation or inhibition), and these distention responsive neurons are sensitive to motilin (291) and ghrelin (157, 504) which, in turn, modulated gastric motility. Furthermore, ARC stimulation increases colonic motility and transit in a manner dependent upon PVN CRF receptors (446, 447) suggesting the possibility of an ARC-PVN circuit that regulates GI functions under physiological (gastric distention) and pathophysiological (stress) conditions.

Amygdala: The amygdala, a paired structure located medially within the temporal lobes, can be subdivided into several distinct subnuclei (principally the basolateral, central, cortical, medial subnuclei), and is part of the limbic system with primary roles in processing emotional and affective responses in addition to its involvement in memory and decision-

making processes. The amygdala displays lateralization, with left and right hemispheres having different roles (Left: sustained emotional and verbal processing, storage and retrieval of emotional memories, activated more by positive emotions. Right: processing of visual and dynamic emotions, declarative and episodic memory, activated more by negative emotions including fear). The amygdala also displays prominent sex-differences, being larger in males but developing over a longer and later time periods, with the left amygdala developing earlier than the right. It is this variability in developmental regulation, and hence potentially network connectivity, that is thought to underlie differences in behaviors and outcomes to emotional and affective inputs. With regard to autonomic functions, the central nucleus of the amygdala (CeA) in particular facilitates processing of emotional information with visceral (including GI) sensory inputs and is knowns to play a prominent role in anxiety and stress-related GI dysfunctions (reviewed in (180, 435).

The CeA receives inputs from brainstem (NTS and ventrolateral medulla; (336, 344, 379)), midbrain (PB complex; (32, 401)), and forebrain (hypothalamus, thalamus, insular cortex (264, 400, 508)) nuclei (Figure 9). In turn, the CeA sends projections to several nuclei involved in the regulation of GI functions, including the hypothalamus, Barringtons Nucleus, LC, and PAG, and the NTS, DMV and ventrolateral medulla (79, 158, 377, 409, 443, 476, 479). It is this extensive connectivity at all supraspinal levels that allows the CeA to play its prominent roles in integrating visceral and somatic inputs with emotional and affective behaviors.

In terms of GI functions, the role of the CeA has been most studied in terms of its effects of stress on GI pathologies. Stimulation of the CeA induces a vagally-dependent increase in gastric acid secretion (184, 236), and stress-induced gastric ulceration is associated with an increase in activity of CeA neurons (174, 178, 179), while lesions of the amygdala attenuated or prevented these stress-induced gastric pathologies (176, 177). Different stressors induce distinct patterns of CeA neuronal activation, with water immersion but not restraint, stress inducing activation of CRF-containing CeA neurons, while cold stress – which also increases gastric acid secretion – did not alter c-fos expression in the CeA (345) suggesting that the emotional valence of the stressors may be responsible for the observed differential effects on gastric outcomes.

In addition to actions to modulate gastric acid secretion, the CeA also regulates gastric motility in response to stress. Depending on the medio-lateral location of the stimulus, activation of the CeA can induce a vagally-dependent increase or decrease in gastric pressure in a manner that involves modulation of gastric-related neurons within the DVC (175, 283). While these earlier studies were conducted in anesthetized rodents, more recent studies using optogenetic manipulations in freely moving mice has confirmed a role for GABAergic CeA projections to the DVC in stress-induced gastric dysmotility and delayed gastric emptying (484). Furthermore, microinjection of orexin-A into the CeA increased gastric motility and accelerated gastric emptying in a vagally-dependent manner in addition to actions to regulate intake of palatable (high fat) food (214), whereas injection of nesfatin-1 – an anorexigenic neuropeptide – decreases gastric motility, again in a vagally-dependent manner (488).

As a major nucleus involved in the integration of visceral afferent inputs with the generation of fear and anxiety behaviors as well as emotional memories, the CeA plays a prominent role in linking stress and anxiety with the development of GI – both gastric and colonic – dysfunction and pathologies (326, 327; Figure 9). Patients with GI hypersensitivity, such as that observed in irritable bowel syndrome (IBS), show increased network connectivity, including greater activation of the amygdala (amongst other central areas including the anterior cingulate cortex and dorsomedial frontal cortex), and decreased adaptation, to colonic or rectal distension (198, 290, 310, 491) while preclinical studies in rodents have demonstrated increased CeA neuronal activation in response to visceral (GI) stimulation (194, 215, 262, 458). At least part of CeA actions to modulate stress- and anxiety-induced outcomes are mediated by activation of the HPA axis; lesion of the CeA decreases the expression and level of CRF within the hypothalamus and decreases HPA axis activation, as evidenced by a decrease in release of ACTH and corticosteroids (165, 413). In turn, corticosteroids can themselves modulate amygdala activity and the response to visceral stimulation. Exposure of the amygdala to increased levels of corticosteroids (via micropellet implanation) increases colonic motility to stress and increases sensitivity to colorectal distension in a manner that appears to depend upon increased CeA CRF levels (159, 326, 455). Similarly, CeA exposure to CRF increases visceral sensitivity, while colonic hypersensitivity is associated with increased levels of CRF within the CeA (165, 413). These stress-induced effects on colonic function are associated with microglial activation and neuronal remodeling within the CeA(289, 511). Importantly from a clinical and translational perspective, environmental enrichment – a paradigm that mimics positive behavioral interventions – inhibits microglial activation within the CeA and reduces chronic stress-induced visceral hypersensitivity, providing a neurobiological basis for the efficacy of interventions such as cognitive behavioral therapy to alleviate stress-induced visceral pain and GI hypersensitivity (341, 512).

Bed Nucleus of the Stria Terminalis: The Bed Nucleus of the Stria Terminalis (BNST), as part of the extended amygdala within the forebrain, also plays a prominent role in the processing and consolidation of behavior and emotions. By relaying information from the CeA to the PVN, the BNST also plays a significant role in regulation of the HPA axis and in autonomic responses to stress (133). As with the amygdala, the BNST receives afferent inputs from nuclei at all supraspinal levels including the brainstem (NTS, ventrolateral medulla, PB complex; (414), midbrain (PAG (414)) and forebrain nuclei (cortex, rostral forebrain structures and thalamus (414), (400, 508)) as well as the CeA itself (249, 367)). The BNST projects to several areas involved in autonomic homeostatic regulation of GI functions including the NTS, DMV, PAG, hypothalamus, LC and PB complex (31, 158, 189). As a result, the BNST is well placed to integrate physiological and behavioral responses (170)(Figure 9).

The BNST, like the CeA, plays a role in the regulation and modulation of GI functions following stress. In contrast to the CeA, however, lesions of the BNST exacerbate gastric lesions induced by stressors (176, 324). The majority of BNST neurons display a GABAergic phenotype (170), and since these inhibitory neurons are the targets of projections from the CeA, the differential effects on gastric acid secretion may involve

the engagement of different CeA output neurocircuits. By virtue of its projections to the hypothalamus, particularly the PVN, the BNST is also strategically positioned to influence HPA axis activity and responses to stress (101, 170). Stress increases the excitability of CRF-immunoreactive BNST ($BNST^{CRF}$) neurons although anatomical studies indicate that the majority of the BNST neurons are GABAergic ($BNST^{GABA}$) including inputs to the PVN (361) suggesting (i) that the BNST exerts a predominantly inhibitory influence over the HPA axis activity and (ii) that activation of the HPA axis may be due to disinhibition of $BNST^{GABA}$ inputs and/or activation of $BNST^{CRF}$ inputs. Certainly, lesions of the BNST are known to increase PVN CRF mRNA levels, activate PVN neurons and increase corticosterone release, suggesting a tonic inhibitory influence over the activity of PVN neurons and downstream HPA axis outcomes (87).

Again, similar to the amygdala, both clinical and preclinical studies have shown the BNST to be sexually dimorphic, being larger in size and neuronal number in males (reviewed in (464)) and the expression of both androgen and estrogen receptors on BNST neurons has implications not only for development but also for the interaction of gonadal hormones with stress-mediated outcomes. During postnatal development, rather than binding to androgen receptors directly, testicular androgens are aromatized to estrogen which acts via Estrogen Receptor α (ERα) to protect neurons from apoptosis, thus increasing volume and neuron number, hence contributing to masculinization of the BNST (464). In adulthood, activation of androgen receptors within the BNST enhances stress induced activation of the PVN and HPA axis (37) both of which may result in GI dysfunction.

Cortex: The increasing awareness of the importance of the brain-gut axis has highlighted the role of the cortex, including cortical influence over the effects of emotional/affective, motivation and reward behaviors as well as memory on the regulation of GI physiological and pathophysiological

GI functions. Various distinct substructures within the cortex influence parasympathetic and sympathetic control over GI functions through descending connections via the hypothalamus and amygdala (see above) as well as via connections to the DVC. Transsynaptic neuronal tracing studies in which rabies virus was injected into the stomach of either vagally intact or vagotomized rats were used to identify cortical neurocircuits regulating parasympathetic vs sympathetic control of the GI tract in rats (268). Cortical networks regulating parasympathetic control of the stomach arise from the insula and medial prefrontal (infralimbic and prelimbic) cortex and project first to the NTS and then the DMV, with a greater density of innervation from the right hemisphere (268, 448, 449) (Figure 10). Indeed, stimulation of the infralimbic cortex induces a vagally-dependent gastroinhibition (195, 348, 508).

In contrast, cortical control over sympathetic outflow to the stomach arises from the primary motor cortex, primary somatosensory cortex, and secondary motor cortex and projects to the RVLM, then to the IML of the spinal cord, and then to the celiac ganglion, again with a greater degree of innervation from the right hemisphere (268).

The insular cortex integrates multiple aspects of sensory processing, including visceral, taste, thermal and nociceptive inputs relayed via the sensory thalamic nuclei. The dense reciprocal interconnectivity of the insular cortex with the limbic system underlies its central role in interoceptive processing (1, 238). In relation to regulation of GI functions, the posterior insular cortex is necessary for the increase in small intestine motility induced in response to feeding (416) as well as taste and gustatory signaling (295). Human imaging studies have also noted structural differences in subregions of the insular cortex (particularly the anterior insular cortex) in woman with IBS suggesting that adverse visceral signaling may be associated with physical changes and altered connectivity in central interoceptive nuclei (24, 162). Chronic GI disorders are associated with mood and behavioral disorders, including depression, anxiety, and cognitive dysregulation (references). The anterior cingulate cortex (ACC) plays critical roles in the emotional responses to anticipation and threat assessment; preclinical studies have shown alterations in ACC structure and connectivity following peripheral neuroinflammation and pain, which exacerbates threat responsiveness and increases anxiety and depression, resulting in further exaggeration of GI pathologies and functions (162, 307). Clinical imaging studies have uncovered network connectivity differences in patients with visceral hypersensitivity or DGBI. For example, IBS patients with visceral hypersensitivity show an increased activity in the anterior cingulate cortex following rectal or colorectal distention (198, 310, 491) while imaging studies in patients with Crohns Disease have shown structural, functional and metabolic alterations (243).

Patients with DGBI such as functional dyspepsia (epigastric pain and/or burning, early satiety, and postprandial fullness in the absence of organic disease) or gastroesophageal reflux disease (GERD) also display impaired cortical responses to gastric stimulation, in which pain responsive regions including the somatosensory cortex (encoding the intensity and location of visceral sensory inputs, including pain) and ventromedial prefrontal cortex are activated, possibly reflecting maladaptive overthinking related to pain or the potential for pain. In contrast, the default mode network (DFN) is deactivated (278, 330, 491, 522). Also known as the default state network or medial frontoparietal network, the DFN is composed of the dorsomedial prefrontal cortex (fear, anxiety) posterior cingulate cortex (emotional/affective responses to pain), precuneus (memory retrieval and visual/mental imagery), and angular gyrus (attention, memory retrieval), and is known to be activated when the brain is at ‘wakeful rest’ and the person is focused inwardly, rather than outwardly, as exemplified by daydreaming or self-reflection, and is negatively correlated with attention networks. Deactivation of the DFN, therefore, often reflects focused attention on the external environment and cognitive processing. Neuroimaging studies of patients with functional dyspepsia, who exhibited greater anxiety and depressions scores compared to health subjects also showed increased network connectivity within the salience network and prefrontal cortex, but lower activity within the DFN network (86). Increased deactivation of the DMN in patients with DGBI, therefore, may indicate increased and focused attention on the GI symptoms, and may be indicative of a broader alteration in cortical structure, function, and connectivity in patients with DGBI, and may provide a neuroanatomical and neurobiological basis for the increased psychological co-morbidities observed in patients with DGBI.

Highlights:

- The hypothalamus has reciprocal connections with the DVC, and plays important roles in the central control of GI responses to stress. Stress decreases gastric emptying in a vagally-dependent manner involving activation of hypothalamic-brainstem CRF neurocircuits. The ability to develop resilience and normalize gastric emptying to stress is dependent upon upregulation of hypothalamic-brainstem OXT neurocircuits
- The amygdala, BNST, insular, and prefrontal cortex are important in the integration of interoceptive and emotional inputs with GI outcomes. Alterations in network connectivity are apparent in both preclinical and human studies, which also suggest structural and functional changes in several cortical and limbic areas in response to visceral hypersensitivity and chronic GI disorders

Conclusions

The advent of new technologies has allowed a more precise and in-depth investigation into the central control of GI functions under both physiological and pathophysiological conditions. Despite that, understanding of complex network connectivity and interplay between different CNS regions and their responses to, and effects upon, the GI tract arguable still lags behind those of other autonomic functions. The location and anatomical structure of the dorsal vagal complex is responsible, at least in part, for some of these issues. The intermingling of cardiovascular, respiratory, and GI reflex networks within the dorsal hindbrain creates problems in truly separating one homeostatic pathway from another, a problem that is compounded by the significant degree of volume transmission between neurons contained within the NTS and DMV. While this is likely to increase overall homeostatic and interoceptive awareness, it also hampers the control and modulation of discrete organ- or reflex- specific neurocircuits. Because the DMV is located ventrally to the NTS, this creates problems when trying to image or record from the DMV in freely moving rodents; implantation of optrodes or GRIN lenses for stimulation or recording necessarily damages or destroys the NTS, AP, or cerebellum, all of which play critical roles in the regulation of preganglionic neurons controlling GI functions. While more recent sequencing studies applied to the DMV have uncovered distinct transcriptional phenotypes of neurons, the roles these neuronal subtypes play in complex GI functions have yet to be uncovered in any real depth.

Regardless, adopting and embracing new technologies will undoubtedly uncover the cellular mechanisms underlying the role of CNS neurons - at all supraspinal levels – in the regulation of GI functions. Comparing and standardizing experimental techniques and technical approaches across different research groups would also greatly assist in easily comparing experimental outcomes; anesthetics are known to differentially affect autonomic outcomes for example, and the extent to which species differences exist in the neuroanatomy and neurobiology of many of the central nuclei discussed above is not elucidated fully.

Both the GI tract and the brainstem (as well as other higher central nuclei) exhibit circadian periodicity; vagal afferent transmission to NTS neurons, for example, fluctuates from day to night suggesting physiological alterations in the 'gain' of visceral sensitivity (370, 371). Similarly, several groups have shown variations in neuronal responsiveness according to nutritional status (fed vs fasting, control vs high fat/high sugar chow, obese vs lean) which should also be borne in mind when conducting and reporting experimental outcomes (346). Developing reproducible disease models should also be a focus for future research within this area. Again, species, and even strain, differences should be borne in mind but – at the same time – understanding such difference may uncover important information regarding both physiology and pathophysiology of the brain-gut axis.

The currently available body of literature serves to highlight the complexity of CNS control over autonomic functions including multiple aspects of GI functions. Understanding such an intricate and interrelated control system and its multiple hierarchies will require multifaceted technical approaches that consider the integration of the GI system as a whole, rather than as discrete and disconnected neurocircuits. Although challenging, such multidisciplinary physiological approaches may be the means by which a combination of basic, translational, and clinical studies uncover new targets for therapeutic intervention into a broad range of pathophysiological processes and diseases.

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Abbreviations

5-HT	5-hydroxytryptophan (serotonin)
ACC	Anterior Cingulate cortex
AHP	afterhyperpolarization
AP	area postrema
ARC	Arcuate Nucleus of the hypothalamus
Barr	Barrington's Nucleus
BLA	Basolateral amygdala
BNST	Bed Nucleus of the Stria Terminalis
CCK	cholecystokinin
CeA	central amygdala

ChAT	choline acetyltransferase
CNS	Central Nervous System
CRF	corticotropin releasing factor
CVLM	Caudal ventrolateral medulla
DFN	Default mode network
DGBI	Disorders of Gut-Brain Interaction
DMV	Dorsal Motor Nucleus of the Vagus
DVC	Dorsovagal Complex
ECC	enterochromaffin cell
EEC	enteroendocrine cell
ENS	Enteric Nervous System
GI	Gastrointestinal
GLP-1	glucagon-like peptide 1
IML	Intermediolateral column of the spinal cord
HPA	Hypothalamic Pituitary Adrenal axis
ICC	Interstitial Cells of Cajal
LC	Locus Ceruleus
LH	Lateral hypothalamus
mGluR	metabotropic glutamate receptor
N.Amb	Nucleus Ambiguus
NANC	non-adrenergic, non-cholinergic
NO	nitric oxide
NTS	Nucleus of the Tractus Solitarius
OXT	oxytocin
PAG	Periaquedutal Gray
PBC	Parabrachial Complex
PBN	Parabrachial Nucleus
PD	Parkinson’s Disease
PDGFR α	Platelet-derived growth factor receptor α

PVN	paraventricular nucleus of the hypothalamus
RVLM	Rostroventrolateral medulla
SCFA	short chain fatty acid
SNpc	Substantia Nigra pars compacta
TLR	Toll-like receptor
TRH	thyrotropin releasing hormone
VIP	vasoactive intestinal peptide

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Clinical Highlights

The enteric nervous system can function independently of extrinsic (sympathetic and parasympathetic) innervation but the extent to which the sympathetic and parasympathetic nervous systems regulate the ENS varies throughout the gastrointestinal tract.

The sympathetic nervous system provides neurovascular control of gastrointestinal blood flow and modulates secretion, sphincter tone, and motility. while the parasympathetic nervous system exerts both excitatory and inhibitory effects on motility, transit, and acid secretion.

The caudal brainstem plays a critical role in regulation of gastrointestinal functions allowing it to integrate ascending interoceptive information with descending modulatory inputs.

The dorsal vagal complex in general, but the area postrema in particular, is a circumventricular organ allowing circulating factors to modulate of vagal neurocircuits regulating gastrointestinal functions more readily.

The interconnectivity of the caudal brainstem with other central nuclei provides an anatomical and functional explanation for the gastrointestinal dysregulation and dysfunction associated with many neurological disorders.

The hypothalamus has reciprocal connections with vagal neurocircuits within the brainstem and plays an important role in the central control of gastrointestinal functions in response to stress.

The limbic system (amygdala, BNST, insular and prefrontal cortex) are important in the integration of interoceptive and emotional responses with gastrointestinal outcomes.

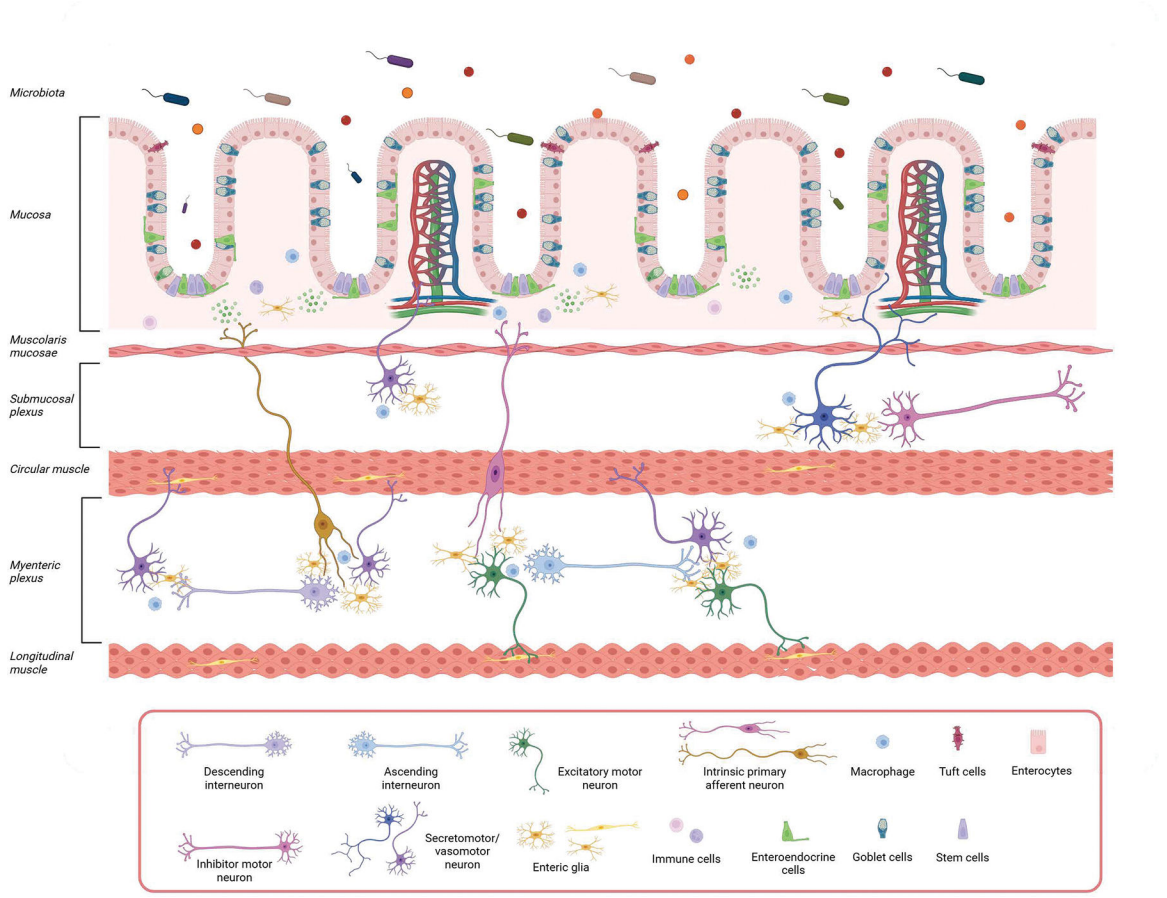

Figure 1. Schematic diagram displaying the enteric nervous system (ENS) structure.

The ENS comprises an integrated network of neurons and glial cells arranged into two ganglionated plexuses, the submucosal plexus located between the muscularis mucosa and circular muscle layer, and the myenteric plexus between the circular and longitudinal muscle layers. These plexuses contain different types of neurons: myenteric/submucosal intrinsic primary afferent neurons; ascending/descending interneurons; excitatory/inhibitory motor neurons; secreto/vaso-motor neurons. Glial cell subtypes are located in the mucosa layer in close proximity to epithelial cells, in both submucosal and myenteric nervous plexuses as well as within the muscular layers.

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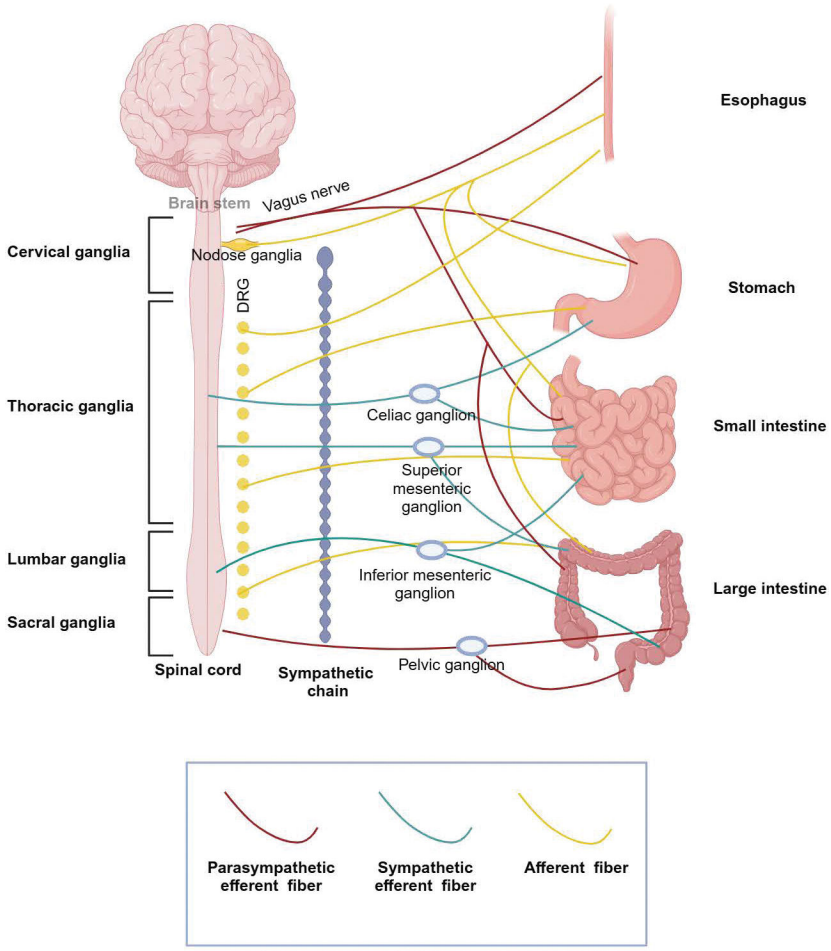

Figure 2. Schematic diagram displaying the afferent and efferent innervation of the gastrointestinal (GI) tract.

Efferent innervation: parasympathetic preganglionic innervation from the vagus and pelvic nerves as well as sympathetic efferent innervation from postganglionic neurons in the abdominal prevertebral ganglia (celiac, superior mesenteric, and inferior mesenteric ganglia) project to the GI tract.

Afferent innervation: vagal afferents have their cell bodies in the nodose ganglia, while spinal afferent nerves with the cell bodies in dorsal root ganglia (DRG) run with the sympathetic and pelvic splanchnic innervations. Note the density of vagal afferent innervation, which is necessary for central relay of interoceptive information, while sympathetic afferents relay predominantly nociceptive information.

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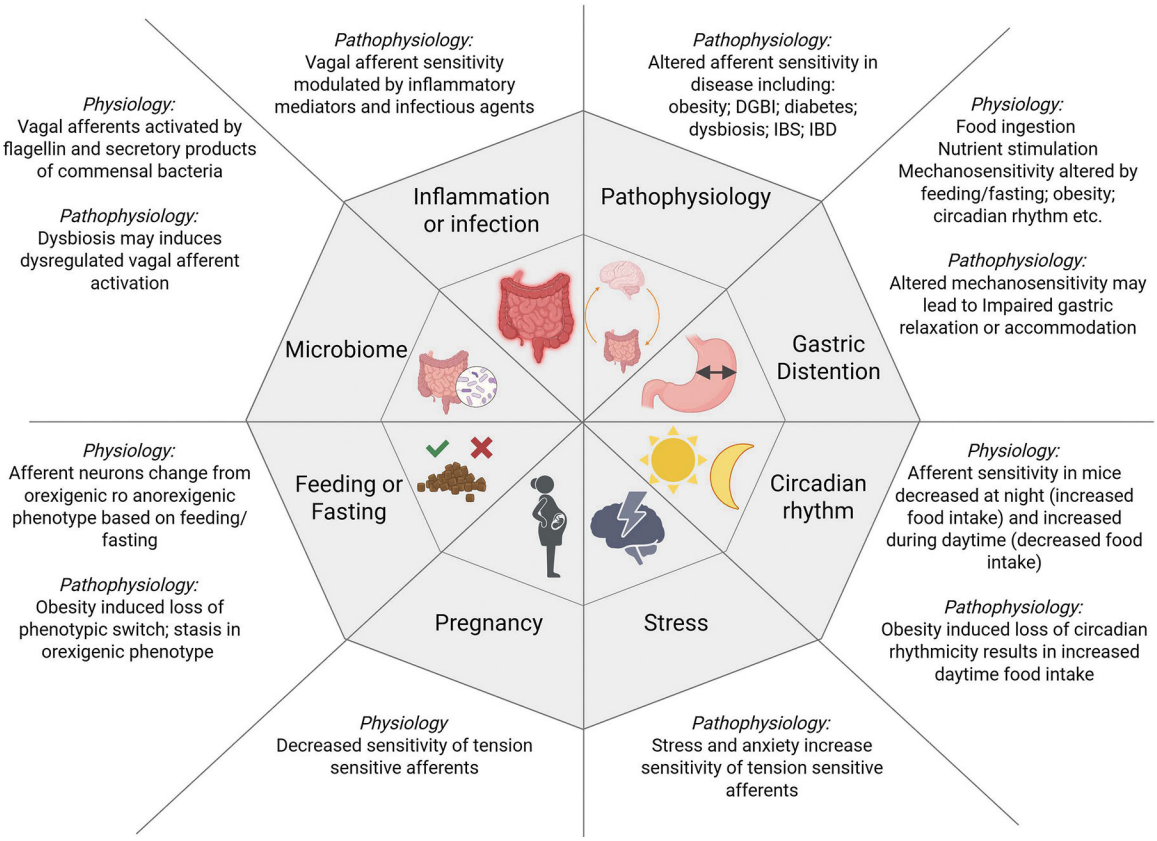

Figure 3: Graphical summary of vagal afferent plasticity

Schematic diagram summarizing changes in vagal afferent sensitivity and responsiveness under physiological and pathophysiological conditions

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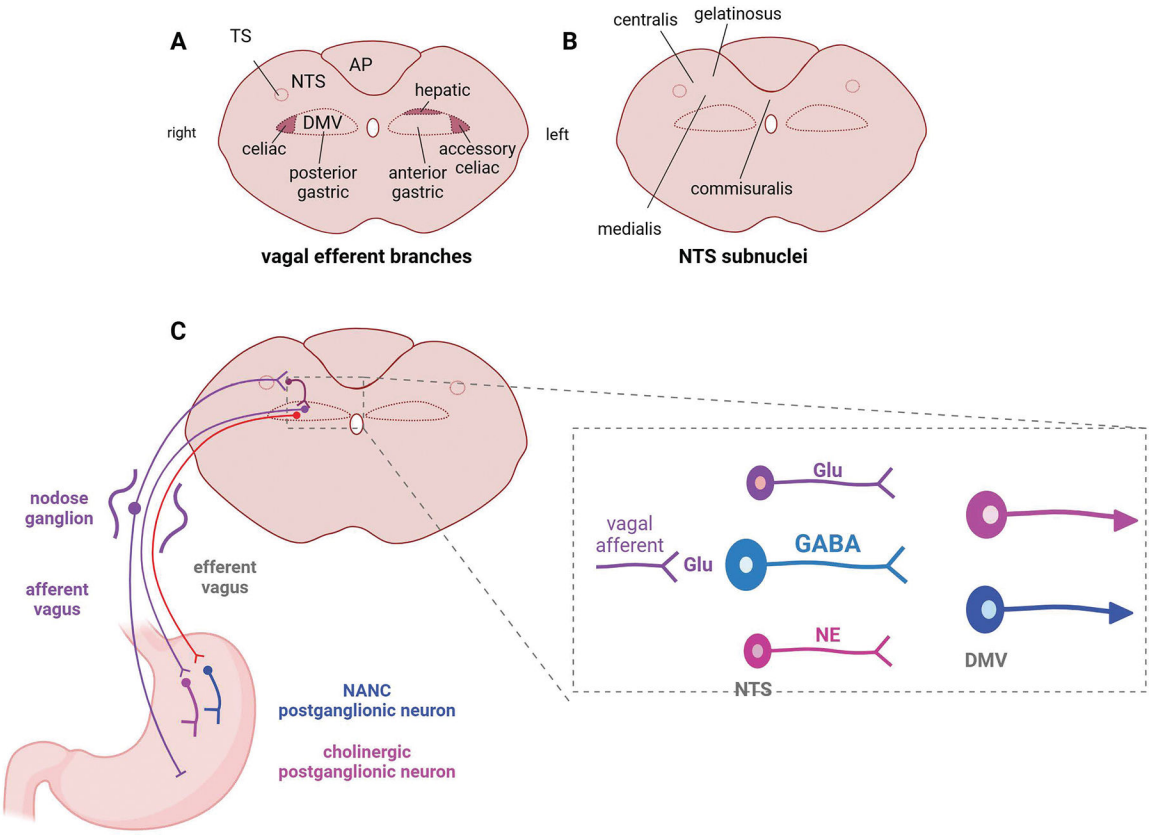

Figure 4: Schematic diagram of brainstem vagal neurocircuits in the rat

A: Vagal motoneurons innervate the viscera via one of five vagal efferent branches. The Anterior gastric, hepatic, and accessory celiac branches are located in the left DMV, while the posterior gastric and celiac are located in the right DMV

B: Vagal afferent projections terminate within the NTS in a broadly viscerotopic manner, with inputs from the GI tract terminating within the gelatinosus and commissuralis subnuclei, while esophageal afferents terminate within the centralis subnucleus. Note, the gelatinosus and centralis subnuclei are present only in the portion of the NTS that is rostral to the AP

C: Vago-vagal reflex schematic. Vagal afferent neurons, whose cell bodies lie within the paired nodose ganglion (or nodose-jugular ganglion complex) are pseudounipolar neurons with a peripheral projection that terminates within the GI tract, and a central terminal that enters the brainstem via the tractus solitarius (TS) and terminates within the NTS. NTS neurons assimilate this visceral sensory information with inputs from the brainstem, midbrain, and forebrain and relayed the integrated response to the adjacent DMV, which contains the preganglionic parasympathetic motoneurons that send the efferent output response back to the GI tract. All DMV neurons are cholinergic and innervate postganglionic neurons within the target organ that form one of two distinct pathways: an excitatory cholinergic pathway and an inhibitory NANC pathway. Inset box highlights the three principle NTS-DMV projections: glutamatergic, GABAergic, and catecholaminergic, of which the inhibitory GABAergic projection is the most prominent under basal conditions. Figure created with BioRender.com under license.

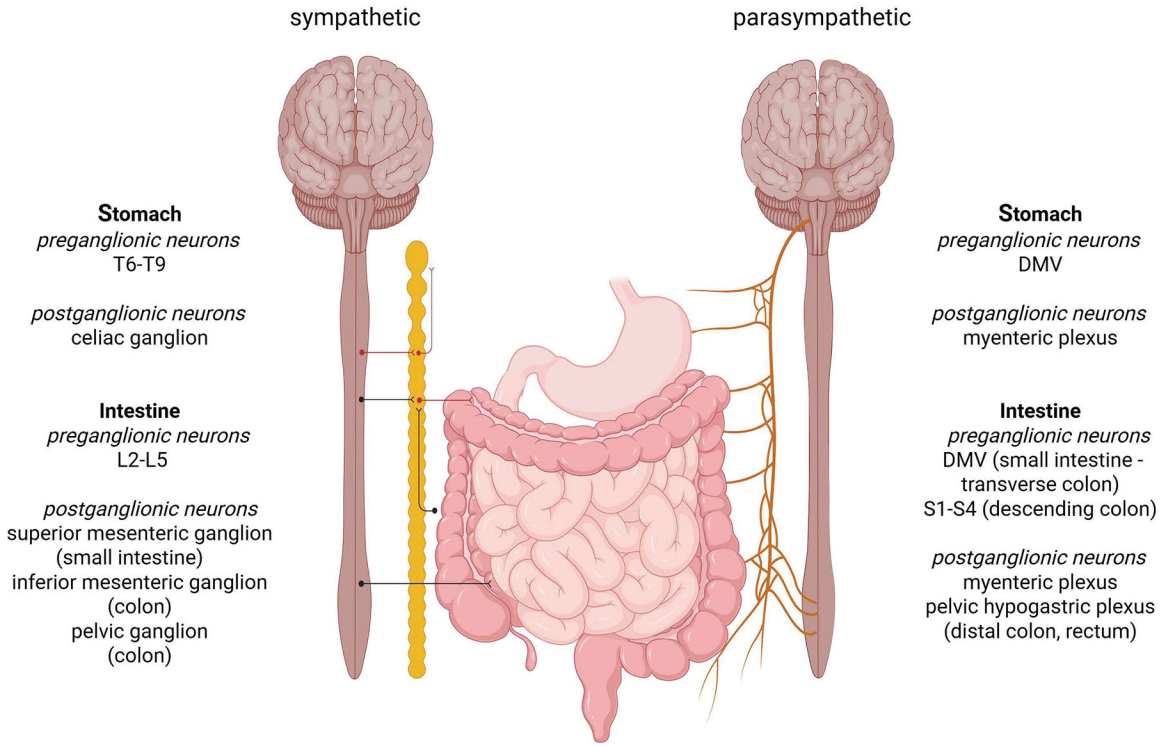

Figure 5: Schematic diagram illustrating the extrinsic innervation to the gastrointestinal tract

Both the sympathetic (left) and parasympathetic (right) nervous systems innervate the gastrointestinal (GI) tract. Preganglionic sympathetic neurons are located in the thoracic (T6-T9; stomach) and lumbar (L2-L5; intestine) spinal cord while postganglionic neurons are located in the celiac (stomach) or superior (small intestine), inferior or pelvic (colon) mesenteric ganglia.

Preganglionic parasympathetic neurons innervating the GI tract are contained within the dorsal motor nucleus of the vagus (DMV; stomach, pancreas, small intestine, and transverse colon) or in the sacral spinal cord (S1-S4; colon). Postganglionic parasympathetic neurons are located within the myenteric plexus of the GI tract, with additional postganglionic neurons innervating the distal colon and rectum being located within the pelvic hypogastric plexus. T = thoracic; L = lumbar; S = sacral

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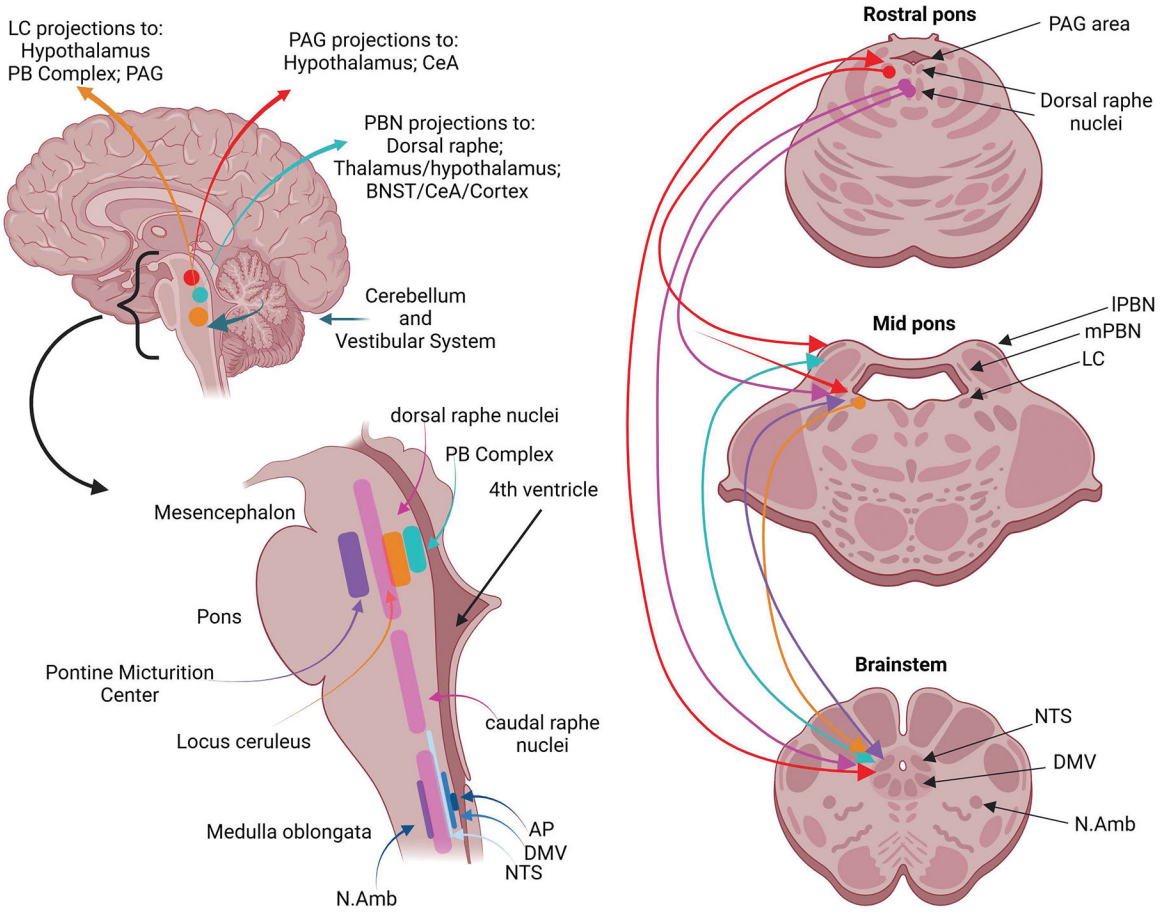

Figure 6: Pontine connections to vagal neurocircuits controlling gastrointestinal functions

Left: Sagittal section and enlargement of the pons showing the broad location of pontine nuclei innervating vagal neurocircuits controlling visceral functions

Right: Coronal sections (rostral, mid, brainstem) showing the major projections of pontine nuclei to vagal neurocircuits

LC, locus ceruleus; PB Complex, parabrachial complex; lPBN, lateral parabrachial nucleus; mPBN, medial parbrachial nucleus; PAG, periaqueductal gray; BNST, bed nucleus of the stria terminals; CeA, central nucleus of the amygdala; AP, area postrema; DMV, dorsal nucleus of the vagus; NTS, nucleus of the tractus solitarius; N.Amb, nucleus ambiguous

Double-headed arrows indicate reciprocal connections.

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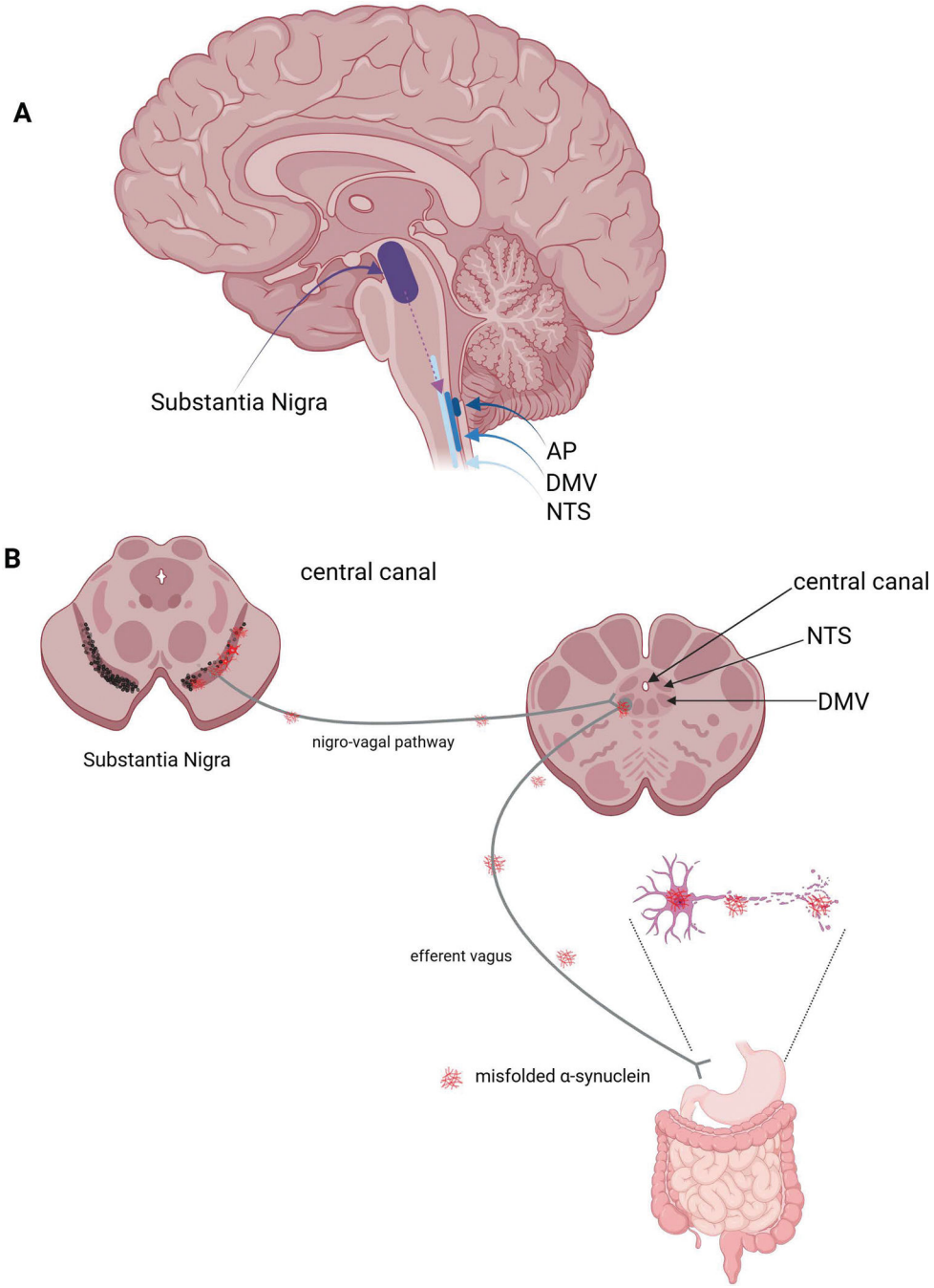

Figure 7: Parkinson's Disease and the gut-brain spread of pathology

A: Schematic diagram of brain (sagittal) showing location of the Substantia Nigra and brainstem vagal nuclei

B: The Braak Hypothesis suggests that misfolded α-synuclein aggregates form within the enteric nervous system and are transported retrogradely to the DMV within the brainstem via the efferent vagus nerve. From there, misfolded α -synuclein is transported via the monosynaptic nigro-vagal pathway to induce neuronal degeneration and loss of dopaminergic neurons within the SNpc.

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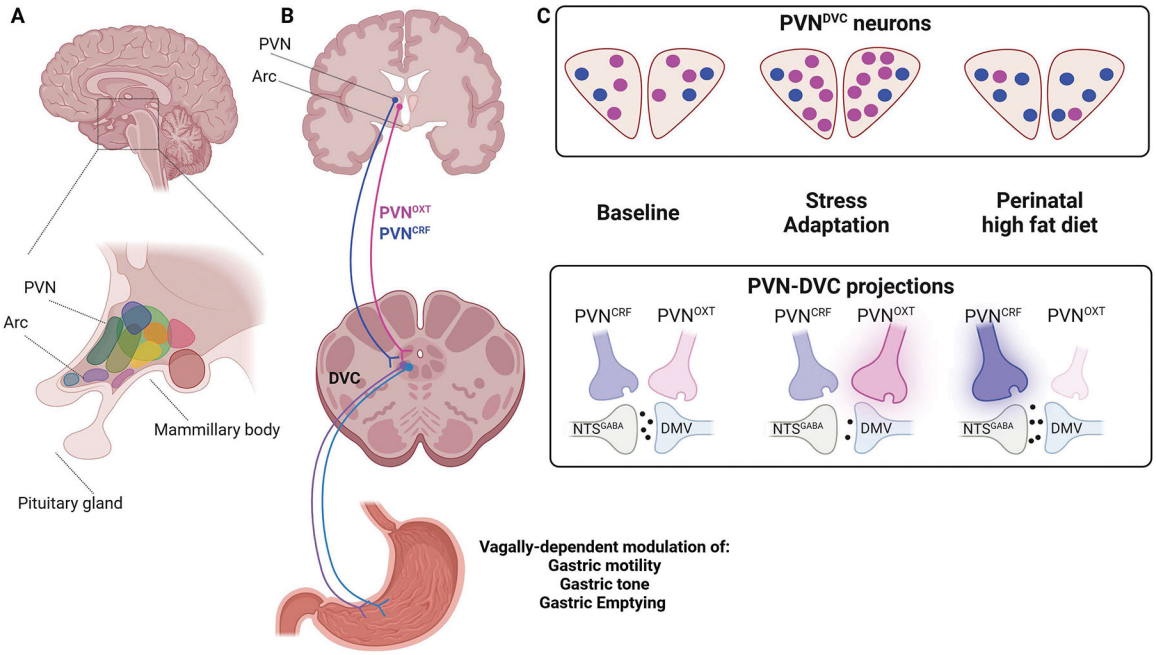

Figure 8: Hypothalamic regulation of vagal neurocircuits controlling gastrointestinal functions

A: Sagittal brain section with expanded area highlighting the hypothalamus and pituitary.

B: Coronal section of the forebrain at the level of the hypothalamus, illustrating descending PVN^{OXT} and PVN^{CRF} projections that terminate in the brainstem at the level of the dorsal vagal complex, and modulate vagal efferent control over the GI tract.

C: Schematic diagram of DVC projecting PVN^{OXT} and PVN^{CRF} neurons and their modulation of NTS-DMV inhibitory transmission. Note that under basal levels, PVN^{OXT} inputs are unable to modulate NTS-DMV GABAergic inhibitory transmission because of the low cAMP-PKA activity within the NTS terminal. Stress induces a vagally-dependent dysregulation of gastric functions, including a delay in gastric emptying. Adaptation to stress (development of resilience) and the restoration of appropriate gastric functions and recovery of gastric emptying rely on upregulation of PVN^{OXT} projections which, because of stress-induced activation of PVN^{CRF} inputs and the activation of adenylate cyclase, are now able to inhibit NTS-DMV GABAergic transmission. Exposure to a high fat diet during the critical perinatal developmental period decreases PVN^{OXT} projections and upregulates PVN^{CRF} inputs, increasing GABAergic inhibition of vagally-dependent efferent control of the stomach similar to that observed during stress.

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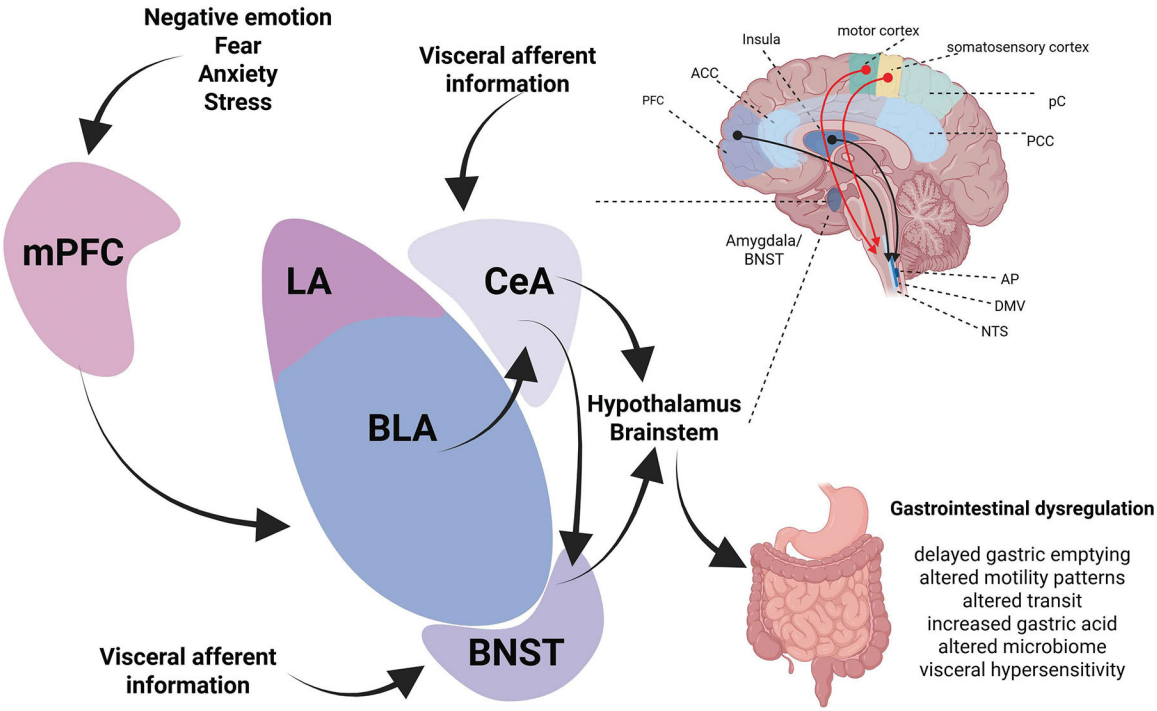

Figure 9: Brain-gut axis and modulation and emotional regulation

Schematic diagram illustrating the cortical networks that influence emotional regulation of GI functions. Response of the medial prefrontal cortex (mPFC) and insular cortex are relayed to, amongst other areas, the amygdala, including the BLA. GABAergic neurons within the BLA project to the CeA via GABAergic interneurons which integrates these inputs with visceral afferent information. The CeA modulates hypothalamic and brainstem activity directly, as well as indirectly via connections from the BNST. The BNST itself also receives visceral afferent information and projects to the hypothalamus and brainstemto modulate GI functions resulting in, amongst others, dysmotility and altered transit, increased acid secretion, microbial alterations, and visceral hypersensitivity.

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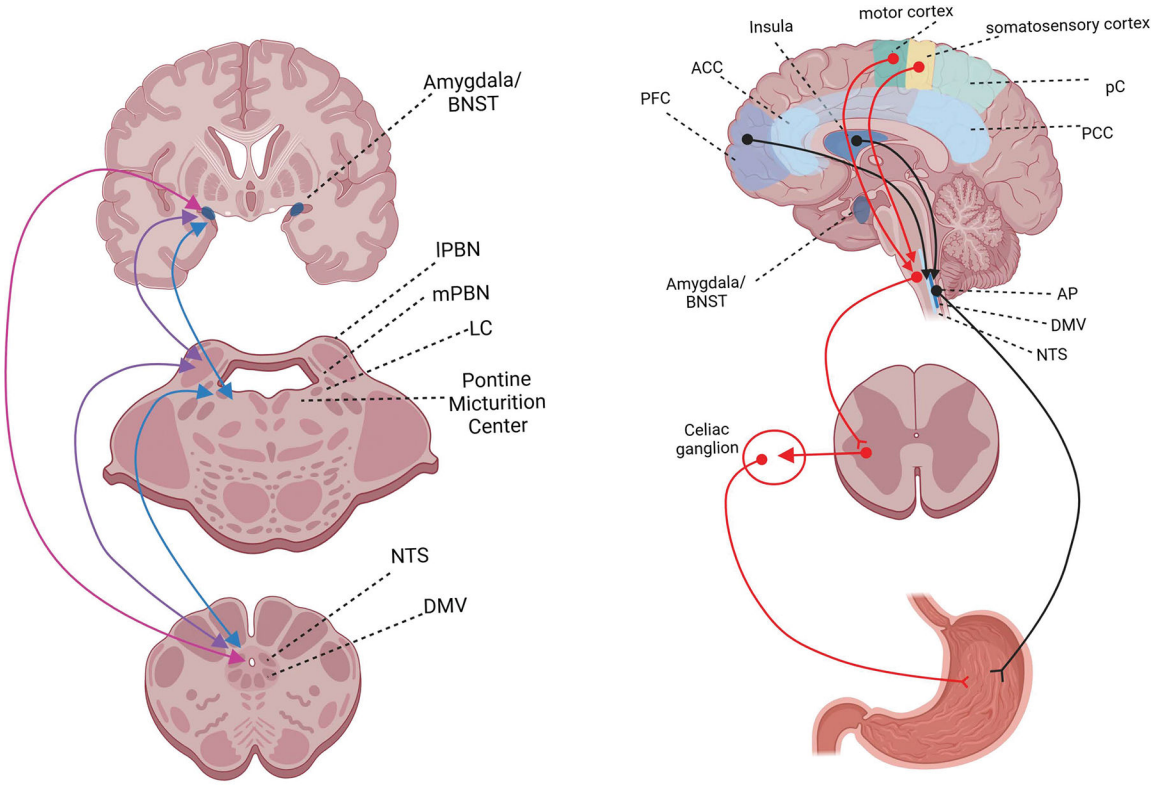

Figure 10: Forebrain regulation of vagal neurocircuits controlling gastrointestinal functions

Left: Coronal section of the cortex illustrating descending connections from the amygdala to the pontine and brainstem nuclei regulating vagal control of gastrointestinal functions

Right: Saggital section of the brain illustrating cortical and limbic descending inputs regulating both sympathetic and parasympathetic control of gastrointestinal functions

Double-headed arrows indicate reciprocal connections.

BNST, bed nucleus of the stria terminalis; lPBN, lateral parabrachial nucleus; rPBN, right parabrachial nucleus; LC, locus ceruleus; AP, area postrema; NTS, nucleus of the tractus solitarius; DMV, dorsal motor nucleus of the vagus; PFC, prefrontal cortex; ACC, anterior cingulate cortex; pC, precuneus; PCC, posterior cingulate cortex

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