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Central Nervous System Control of Gastrointestinal Motility and Secretion and Modulation of Gastrointestinal Functions

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Abstract

Although the gastrointestinal (GI) tract possesses intrinsic neural plexuses that allow a significant degree of autonomy over GI functions, the central nervous system (CNS) provides extrinsic neural inputs that regulate, modulate, and control these functions. While the intestines are capable of functioning in the absence of extrinsic inputs, the stomach and esophagus are much more dependent upon extrinsic neural inputs, particularly from parasympathetic and sympathetic pathways. The sympathetic nervous system exerts a predominantly inhibitory effect upon GI muscle and provides a tonic inhibitory influence over mucosal secretion while, at the same time, regulates GI blood flow via neurally mediated vasoconstriction. The parasympathetic nervous system, in contrast, exerts both excitatory and inhibitory control over gastric and intestinal tone and motility. Although GI functions are controlled by the autonomic nervous system and occur, by and large, independently of conscious perception, it is clear that the higher CNS centers influence homeostatic control as well as cognitive and behavioral functions. This review will describe the basic neural circuitry of extrinsic inputs to the GI tract as well as the major CNS nuclei that innervate and modulate the activity of these pathways. The role of CNS-centered reflexes in the regulation of GI functions will be discussed as will modulation of these reflexes under both physiological and pathophysiological conditions. Finally, future directions within the field will be discussed in terms of important questions that remain to be resolved and advances in technology that may help provide these answers.

Introduction

While the gastrointestinal (GI) tract possesses intrinsic neural plexuses that allow a significant degree of autonomy over functions including digestion, nutrient absorption and the elimination of waste, the central nervous system (CNS) provides extrinsic neural inputs that regulate, modulate, and control these functions. The small and large intestines display a considerable degree of independent neural control and are capable of functioning in the absence of extrinsic neural inputs. The stomach and esophagus, in contrast, are much more dependent upon extrinsic neural inputs, particularly from parasympathetic and sympathetic pathways that derive from, or are controlled by, nuclei located in the caudal brainstem. Removal of the extrinsic innervation to the stomach results in disorganized and dysregulated

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gastric activity that frequently results in symptoms such as nausea and vomiting, abdominal discomfort and pain, and diarrhea. Remarkably, however, gastric activity regains a degree of normality after a period of time suggesting that the role of the extrinsic neural inputs to the stomach are to co-ordinate and regulate the GI tract in a more widespread and integrated manner to maintain appropriate homeostatic control over digestive functions.

The sympathetic nervous system exerts a predominantly inhibitory effect upon GI muscle and provides a tonic inhibitory influence over mucosal secretion while, at the same time, regulates GI blood flow via neurally mediated vasoconstriction. The parasympathetic nervous system, in contrast, exerts both excitatory and inhibitory control over gastric and intestinal tone and motility (i.e., milling, absorption, secretion, and defecation), implying a more finely tuned and complex influence over GI activity. Although GI functions are controlled by the autonomic nervous system and occur, by and large, independently of conscious perception, it is clear that the sympathetic and parasympathetic regulation and modulation of the GI tract are modulated by higher CNS centers that influence homeostatic control as well as cognitive and behavioral functions.

This review will describe the basic neural circuitry of the parasympathetic and sympathetic neural inputs to the GI tract as well as the major CNS nuclei that innervate and modulate the activity of these pathways. The role of CNS-centered reflexes in the regulation of GI functions will be discussed as will modulation of these reflexes under both physiological and pathophysiological conditions. Finally, future directions within the field will be discussed in terms of important questions that remain to be resolved and advances in technology that may help provide these answers. A list of abbreviations can be found in Table 1.

Parasympathetic innervation to the stomach and upper intestine

Parasympathetic innervation to the stomach, small intestine and proximal colon is supplied by the vagus nerve. Neuronal tracing techniques have shown that the preganglionic motoneurons that provide vagal innervation to the stomach and intestine originate in the dorsal motor nucleus of the vagus (DMV) within the brainstem (10, 11, 48, 49, 257, 437). The stomach receives an especially dense parasympathetic vagal innervation which decreases distally and becomes sparse as one progresses distally through the colon (11, 48, 49). The pharynx and larynx, in contrast, are innervated by preganglionic motoneurons located within the compact as well as the external formation of the nucleus ambiguus. The location of preganglionic neurons innervating the esophagus is species specific and dependent upon whether the esophagus is composed of smooth muscle (cat, rabbit, ferret, and human; originating in the DMV) or striated muscle (rat; originating in the nucleus ambiguus).

Vagal efferent motoneurons

Of the preganglionic parasympathetic motoneurons innervating GI organs, those located within the DMV have been studied most extensively. Rather than being organized in a viscerotopic or organotopic manner, they are organized in “columns” that extend throughout the rostro-caudal extent of the nucleus, and innervate the GI tract through each of the five

subdiaphragmatic branches (anterior gastric, posterior gastric, hepatic, celiac, and accessory celiac) (168, 354, 437) which are organized in a medio-lateral arrangement within the brainstem nucleus. DMV neurons with axons projecting via the celiac and accessory celiac vagal branches, for example, are located within the lateral tips of the DMV whereas the cell bodies of axons projecting via the gastric branches are located within the medial left (anterior gastric branch) or right (posterior gastric branch) DMV. Such a level of organization is not maintained peripherally, however; the stomach is innervated by both gastric branches and the hepatic vagal branch, originating in the left DMV, while the duodenum is innervated by all vagal branches. The colon is innervated by both celiac and accessory celiac vagal branches although the density of this innervation decreases distally such that while approximately 65% of myenteric neurons within the cecum receive vagal efferent innervation, less than 20% of neurons in the descending colon are innervated by the efferent vagus (11, 48).

As preganglionic parasympathetic neurons, all DMV neurons are *a priori* cholinergic and release acetylcholine to activate nicotinic receptors present on postganglionic neurons within the target organ of interest [in this instance, Interstitial Cells of Cajal (ICC) and myenteric neurons within the stomach and upper intestine; reviewed in (422)]. Previously, it was thought that DMV neurons contacted specific “command neurons” within the enteric nervous system to modulate and influence hard-wired motor programs. Several morphological and functional studies have suggested, however, that most enteric neurons receive inputs from vagal fibers and that individual vagal fibers contact many enteric neurons (432, 526) suggesting that the role of the vagus is a more generalized modulation of existing activity levels within enteric neural circuits. Neurotransmitters other than acetylcholine have also been identified within vagal preganglionic neurons within the brainstem, including catecholamines and NO (207, 242, 256, 551); vagal neurotransmission is essentially prevented by nicotinic acetylcholine receptor antagonists, however, suggesting that these noncholinergic neurotransmitters play a modulatory role in cholinergic vagal transmission (432).

Postganglionic neurons within the stomach and upper intestine contacted by vagal efferent fibers form two distinct pathways, though, which allow a very precise, finely tuned control of GI functions. An excitatory cholinergic pathway allows smooth muscle contraction via activation of muscarinic cholinergic receptors on GI smooth muscle whereas a non-adrenergic, non-cholinergic (NANC) pathways allows smooth muscle relaxation via release of predominantly nitric oxide and/or vasoactive intestinal polypeptide (reviewed in (499). Technical constraints have meant that, to date, the vast majority of data on rodents gastric tone and motility has been generated in anesthetized animals; under these conditions, the excitatory cholinergic pathway appears to predominate. In fact, systemic administration of the muscarinic antagonist, atropine, reduces gastric tone and motility dramatically, whereas systemic administration of a NO synthase inhibitor has lesser effect to increase gastric tone and motility. Neurally mediated gastric relaxation, therefore, may be achieved via either withdrawal or inhibition of the tonic excitatory cholinergic pathway or activation of the inhibitory NANC pathway (499).

In contrast, gastric secretion is regulated via vagal inputs to postganglionic neurons that regulate parietal cell activity via postganglionic excitatory muscarinic pathway and a direct inhibition following vagal activation has not been observed (433, 434). The influence of the CNS over gastric secretion was famously first described by William Beaumont in 1833 [reprinted with editorial comments by Combe (40)] who noted that the acid secretion was affected by "fear, anger, and whatever depresses or disturbs the nervous system." The role of the vagus nerve in gastric secretion was later confirmed by Pavlov in 1902 who noted that the cephalic phase of acid secretion is mediated entirely by the vagus nerve. In contrast, the gastric and intestinal phases of acid secretion involve the activation of both vagal and spinal reflexes in response to GI distention and/or the activation of mucosal receptors [reviewed in (270)]. Neurophysiological studies, notably electrical stimulation or lesion of discrete central nuclei, have highlighted the role of several areas within the brain in the control of gastric acid secretion, particularly the hypothalamus (lateral, ventromedial, and paraventricular nuclei), the locus coeruleus (LC), the caudal medullary raphe nuclei and the amygdala, as discussed in more detail below.

In contrast to the relatively extensive information regarding the central modulation of gastric acid secretion, far less information is available regarding the central control of other gastric secretions, particularly enzyme and mucus secretion. Activation of the caudal raphe nuclei increases gastric pepsin secretion in anesthetized animals in a vagally dependent manner (535). Similarly, stimulation of the DVC induces gastric prostaglandin release, which appears to play a significant role in gastric mucosal protection in response to stress (43, 107, 459).

Properties and organization of vagal efferent motoneurons

Despite the lack of strict viscerotopic organization within the brainstem, DMV neurons appear to exhibit a more function-specific configuration. DMV neurons involved in the inhibitory NANC pathway, for example, appear to be located more caudally within the brainstem, in contrast to DMV neurons within the excitatory cholinergic pathway which appear to be located in the medial and rostral areas of the nucleus (116, 275, 411, 412). Furthermore, Huang et al., have suggested that within the human brainstem, DMV neurons display distinctive morphological properties and are organized into functionally specific groups that innervate particular visceral organs (239). In support of this, studies in rodents have demonstrated that DMV neurons are morphologically heterogeneous (74, 169, 252, 317) and our studies have shown that the biophysical and morphological properties of DMV neurons are correlated with their target organ within the GI tract (74). In brief, it appears that DMV neurons projecting to the gastric fundus are smaller and have fewer dendritic branches as compared to other GI-projecting DMV neurons, with neurons projecting to the large intestine having the largest soma size (74,317). In addition, functional studies have also demonstrated that DMV neurons sensitive to gastric distention are morphologically different from those that respond to intestinal distention (164). It seems likely, therefore, that the properties of DMV neurons are influenced by, or even dependent upon, their function and efferent target.

DMV neurons are also heterogeneous with respect to their membrane properties; several studies have demonstrated that membrane currents are distributed unevenly within DMV neuronal populations (74, 420, 421, 494) and the presence or absence of these currents appears to play prominent roles in determining the excitability of DMV neurons. For example, we have shown that DMV neurons projecting to the stomach are more excitable and fire more action potentials in response to depolarizing current injections as compared to neurons projecting to the intestine (74). In part, this difference appears due to the presence of a smaller and faster action potential afterhyperpolarization in gastric-projecting neurons. While, in DMV neurons, this afterhyperpolarization is due primarily to activation of an apamin-sensitive (SK) calcium-dependent potassium current (74, 420, 421), we have shown recently that damage to DMV neurons, either by distal nerve section (vagotomy) or by perivagal capsaicin application induces the expression of a previously undetectable charybdotoxin-sensitive (BK) calcium-dependent potassium current (70). This would suggest that the intrinsic membrane properties of DMV neurons innervating the GI tract are not static but, rather, are open to expression changes in response to damage or insult.

The smaller and faster action potential afterhyperpolarization in gastric-projecting DMV neurons, coupled with their lower membrane input resistance (74) implies that, compared to intestinal-projecting neurons, they are more liable to respond to changes in synaptic inputs. This is of particular importance when one considers that DMV neurons are tonically active and fire action potentials spontaneously at a low frequency (~1 Hz) (22, 316, 494, 496). Minor changes in synaptic inputs or membrane currents, therefore, can have dramatic effects upon neuronal firing patterns hence vagal efferent outflow.

The activity of DMV neurons, and hence vagal efferent activity, is also regulated by synaptic inputs from several brainstem and higher CNS nuclei. As mentioned previously, gastric functions have been studied most commonly in anesthetized animals; under these “basal” conditions, the activity of DMV neurons innervating the GI tract is regulated by an ongoing, tonic inhibitory GABAergic input (22, 175, 447, 496). The majority of these inhibitory inputs arise from the adjacent nucleus tractus solitarius [NTS; (499)] although DMV neurons also receive innervation from several other brainstem and higher CNS nuclei (see below). While DMV neurons also receive excitatory glutamatergic and catecholaminergic inputs from the NTS, they do not appear to be as critical in regulating the tonic activity of vagal efferent motoneurons (412, 447). It is also important to note, at this point, that several morphological studies have shown that the dendritic projections of DMV neurons can extend into the NTS, the area postrema and even penetrate the ependymal layer of the fourth ventricle (407, 437) suggesting that vagal motoneurons are capable of responding to circulating factors directly. Additionally, the brainstem area containing the dorsal vagal complex (DVC, i.e., DMV, NTS, and area postrema) is essentially a circumventricular organ, lying ventral to the fourth ventricle and is highly vascularized with fenestrated capillaries (111, 171). An additional layer of neurons, termed subependymal cerebrospinal containing neurons (CSF-cNs) are positioned, strategically, between the CSF and neuronal parenchyma and potentially integrate CSF signaling with autonomic homeostatic signaling (361). Indeed, we have demonstrated previously that brainstem neurons can be excited following peripheral administration of the GI neurohormone, cholecystokinin (CCK) even after surgical removal

of vagal afferent input to the brainstem (31) implying that the activity of central vagal neurons, including DMV neurons, may be modulated directly by circulating factors.

The DVC is innervated by several brainstem and higher CNS centers involved in autonomic regulation. NTS neurons, which provide the most prominent source of synaptic inputs to GI-projecting DMV neurons, play a critical role in shaping the activity of the efferent vagus nerve (Fig. 1). In addition to their involvement in vagal autonomic neurocircuits via their projections to vagal efferent motoneurons, NTS neurons are also the recipient of inputs from vagal afferent (sensory) fibers that innervate the thoracic and abdominal viscera. Indeed, while the vagus is a mixed sensory/motor nerve, it is predominantly sensory with 70% to 80% of vagal fibers being of sensory origin depending on the species (reviewed in (52)). Vagal afferents that transduce and relay information from the GI tract can be classified based upon their response to distention or pressure (principally low-threshold, although nociceptive high-threshold fibers also exist), the location of their receptive fields (mucosal, muscle, or serosal/mesenteric), their preferred stimulus modality (chemical, osmotic, mechanical, both in-series and in-parallel) or the region of GI tract innervated [reviewed in (52)]. Regardless of their sensory modality or function, the cell bodies of these vagal afferent fibers lie within the nodose ganglia (or nodose-petrosal-jugular ganglion complex) and their central terminals enter the brainstem via the tractus solitarius, and impinge, principally, onto NTS neurons. Within the NTS, neurons are organized in subnuclei which display a viscerotopic manner relative to their afferent inputs (10, 12, 36). Gastric vagal afferents, for example, innervate neurons within the NTS gelatinosus and commisuralis while esophageal afferents innervate neurons within the NTS centralis (10, 69). While cardiovascular and respiratory afferents innervate neurons within the medial and ventrolateral NTS (333, 400), it is important to recognize that the dendritic projections of NTS extent throughout the nucleus and intermingle within the various subnuclei [reviewed in (253)] providing a potential means by which homeostatic reflexes may be co-ordinated across autonomic organs.

The central terminals of vagal afferent fibers innervate NTS neurons and use principally glutamate as a neurotransmitter (13–15,18,32,62). While activation of ionotropic glutamate receptors (NMDA and non-NMDA receptors) is critical in the transmission of visceral information to the NTS, several metabotropic receptors (mGluR) have also been identified within the DVC. Receptors from all three subtype groups of mGluR have been identified within the DVC (20,79,102,103, 186–189, 255). Group I mGluR are predominantly located postsynaptically (212) while Group II and group III mGluR are predominantly at presynaptic sites and modulate synaptic transmission (20, 79, 102, 186, 188, 211, 546). The presence of and location of mGluR within central vagal neurocircuits suggests that the glutamate released from vagal afferent terminals, in addition to relaying vagal afferent information, may also exert a longer term, more modulatory role over the activity of vagal neurocircuits.

Modulation of DMV neuronal activity

Studies from several groups, including our own, have shown that the excitability of DMV neurons can be modulated by numerous neurotransmitters, neurohormones, and

neuromodulators that act either directly on the DMV neuronal membrane or indirectly, to modulate the activity of synaptic inputs, including several neuroactive substances known to be involved in the central modulation of GI functions such as serotonin (75,495), dopamine (90,550), norepinephrine (NE) (50, 318), opioid peptides (72, 73, 402), orexin (192), oxytocin (86, 229), corticotropin releasing factor (291, 460, 501), endocannabinoids (138, 185), neurokinins (281, 284, 292), CCK (32,83,231,549), thyrotropin-releasing hormone [TRH; (70,497)] and glucagon-like peptide 1 (71, 228).

The response of vagal motoneurons to neurotransmitters or neuromodulators does not appear to be static, however. Recent evidence from several laboratories, including our own, has shown that a significant degree of plasticity with vagal neurocircuits occurs in response to physiological or pathophysiological conditions. For example, while GABAergic projections from the NTS-DMV exert the most significant influence over DMV neuronal activity, hence vagal efferent output, only a few neurotransmitters or neuromodulators have been shown to modulate GABAergic synaptic transmission to GI-projecting DMV neurons while the majority of transmitters/modulators are able to regulate glutamatergic synaptic transmission (72, 75, 77, 128, 137, 138). Presynaptic inhibitory effects of many of these neurotransmitters or modulators can be induced, however, following activation of the cAMP-protein kinase A (PKA) pathway within brainstem neurocircuits either by direct activation of cAMP by forskolin or indirect activation via treatment with neurohormones such as TRH, CCK, or GLP-1, which are known to be involved in digestive functions and that act on receptors positively coupled to adenylate cyclase. Activation of the cAMP-PKA pathway appears to induce trafficking of receptors to GABAergic terminals allowing modulation of inhibitory synaptic transmission to be uncovered (73, 76, 80).

Further investigations revealed the mechanism behind this apparent disparity between glutamatergic and GABAergic synaptic transmission; GABAergic nerve terminals impinging upon GI-projecting DMV neurons contain group II mGluR that are tonically active via glutamate released from monosynaptic vagal afferent terminals (79). Activation of these presynaptic group II mGluR decreases cAMP levels within GABAergic nerve terminals, preventing the actions of neurotransmitters/modulators negatively coupled to adenylate cyclase (e.g., 5-HT_{1A}, NPY/PYY Y_1 and Y_2, α-2-, and μ-opioid receptors) from exerting any modulation over inhibitory synaptic transmission. Preventing activation of these group II mGluR, either by surgically removing vagal afferent inputs to the brainstem, or by administration of selective group II mGluR antagonists, increases cAMP levels, activates a cAMP-PKA cascade, and uncovers presynaptic inhibitory actions of these neurotransmitters/modulators (79, 80, 84). In contrast, while excitatory glutamatergic terminals impinging upon GI-projecting DMV neurons display functional group II and group III mGluR, they are not active tonically, hence, cAMP levels within excitatory terminals are higher and the same neurotransmitters/modulators can regulate glutamatergic synaptic transmission (79).

This suggests that ongoing vagal afferent activity plays a prominent role in setting the “tone” or “state of activation” of vagal brainstem neurocircuits by regulating the ability of GABAergic neurotransmission to be modulated. Decreasing vagal afferent input, either by inhibiting their activation, or by damage to vagal fibers, would be expected to alter the “gain” of vagal efferent output by allowing modulation of the tonic GABAergic input

controlling DMV neuronal activity. In addition, neurohormones and neuromodulators involved in the regulation of gastric functions such as CCK, GLP-1, and CRF, which act to activate adenylate cyclase, directly overcome the effects of group II mGluR to decrease cAMP levels within GABAergic terminals, will similarly alter the “gain” of vagal efferent output [reviewed in (78, 81, 82)].

To date, plasticity within central vagal neurocircuits in response to modulation of the cAMP-PKA second messenger system has certainly been studied in the greatest detail. To assume this is the only second messenger system that can modulate the response and activation of central vagal neurocircuits, however, would appear to be unreasonably simplistic. It would appear a far more realistic proposition to assume that other second messenger systems are equally capable of modulating the “state of activation” of central vagal neurocircuits, hence correspondingly capable of modulating vagal efferent control of GI functions.

Parasympathetic control of the colon

While the vagus nerve provides innervation to the proximal colon, the majority of parasympathetic innervation to the distal colon originates from preganglionic neurons within the lumbosacral spinal cord, prominently from S1–S4 regions (11, 51, 129, 348, 357, 525). These sacral preganglionic neurons form a continuous band of cells deep within the dorsal intermediolateral (IML) column and are smaller and spatially separate from those preganglionic neurons innervating the bladder [reviewed in (249)]. While preganglionic neurons innervating the colon are, as elsewhere, cholinergic, immunohistochemical studies have identified populations of preganglionic parasympathetic enkephalinergic neurons within the S2–S3 segments of the sacral spinal cord of the rat and cat (190, 262). While it is not known whether these enkephalinergic neurons are involved in parasympathetic regulation of colonic motility, opioid peptides have been shown to act presynaptically to modulate acetylcholine release from colonic-projecting preganglionic neurons (265) suggesting that neurally mediated release of enkephalins may modulate cholinergic transmission.

Regardless of their neurochemical phenotype, the axons of preganglionic parasympathetic neurons follow two pathways from the spinal cord to the colon; neurons either innervate postganglionic neurons within the myenteric plexus directly, or they innervate postganglionic neurons within ganglia of the pelvic (hypogastric) plexus (178, 282). Neurons of the pelvic ganglia then innervate neurons within the myenteric plexus of the distal colon and rectum via the rectal nerves. As reported for the parasympathetic innervation of the stomach and upper intestine, there appears to be a dual parasympathetic control of the colon. Stimulation of the pelvic or rectal nerves induces either (i) an increase in motility, via activation of an atropine-sensitive, cholinergic pathways, or (ii) an inhibition of motility, via activation of an atropine-insensitive, NANC pathway (155) that possibly involves release of nitric oxide or purines (267, 357, 518).

The parasympathetic neural innervation to the colon plays a significant role in regulating propulsive colonic motility, particular prior to defecation. Damage to parasympathetic nerves, or extrinsic denervation, frequently results in dysregulated colonic motility and

constipation. As following extrinsic denervation of the stomach, however, over time colonic motility patterns may be somewhat restored suggesting the role of parasympathetic inputs is to enhance and modulate intrinsic motility patterns rather than initiate or terminate colonic functions.

Sympathetic control of the gastrointestinal tract

Sympathetic preganglionic neurons innervating the GI tract arise from the thoracic and lumbar spinal cord. The majority of neurons innervating the stomach arise from T6–T9 thoracic levels while neurons innervating the colon arise predominantly from spinal L2–L5 lumbar levels, depending on the species, although in humans some neurons may reside within the caudal thoracic segments. As with all preganglionic neurons, these sympathetic neurons are cholinergic, but several reports also describe the presence of small neuropeptides which may exert a modulatory influence of cholinergic transmission. Sympathetic preganglionic neurons activate postganglionic neurons that are contained within well-defined ganglia outside of the stomach and intestine. Most sympathetic postganglionic neurons innervating the GI tract are contained within prevertebral ganglia although some fibers can arise from neurons within paravertebral ganglia (sympathetic chain ganglia) [see (446) for review]. Postganglionic sympathetic neurons innervating the stomach are contained within the celiac ganglion, while neurons innervating the intestine reside in the superior mesenteric ganglion (small intestine), the inferior mesenteric ganglion (colon) or pelvic ganglion (colon). [NB—pelvic ganglia, therefore, are rather unique in that they contain the cell bodies of both postganglionic sympathetic and parasympathetic neurons. Cross-talk between these neurons allows for integration between sympathetic and parasympathetic regulation of the colon; (249).] Postganglionic sympathetic neurons use NE as their primary neurotransmitter although release of neuropeptides, including neuropeptide Y (NPY), somatostatin, and galanin, as well as purines have been described [reviewed in (247)].

Historically, Eduard Pflüger (1857) was the first to note that activation of the splanchnic sympathetic innervation to the GI tract inhibited motility but constricted sphincters [reviewed more recently in (247,305)]. While sympathetic fibers provide a dense innervation to sphincters, and induce constriction via a direct action on smooth muscle, innervation to circular and longitudinal smooth muscle is relatively sparse. Sympathetic fibers innervate principally enteric neurons (both myenteric and submucosal) and, with the advent of neural recording techniques, it was demonstrated that the sympathetic fibers can act pre- and postsynaptically to modulate the activity of enteric neurons either via direct actions on the enteric neuronal membrane (65, 355, 438, 467) or indirectly, via actions to modulate neurotransmitter release (226,438,467,524). The vascular bed of the entire GI tract is densely innervated by sympathetic fibers and regulation of GI vascular tone is an important modulator of blood pressure (195).

More recently, sympathetic innervation of gut-associated lymphoid tissue and modulation of GI immune function has been described. Sympathetic fibers innervate Peyer’s patches within the intestine (156) and macrophages (377) providing a potential means by which immune functions can be modulated. Enteric glial cells are also innervated by sympathetic

fibers; while the precise role of enteric glia is unclear, they are known to respond to ATP released by sympathetic fibers which suggests a means by which the activity and functions of enteric neurons may be integrated and modulated (203–205).

Despite the dense sympathetic innervation to the GI tract, there appears to be little tonic sympathetic activity, at least with regard to GI motility although splanchnic nerve section does result in an moderate increase in peristaltic activity (38,39). Sympathetic fibers do provide a tonic level of activity to vasoconstrictor and secretomotor neurons, however; sympathectomy increases GI secretion (540) while stimulation of sympathetic nerves or exogenous application of NE increases fluid absorption, independently of alterations in vascular tone (197, 367), providing a means by which fluid secretion or absorption can be modulated, as required, by alterations in sympathetic tone. The activity of sympathetic motor and secretomotor neurons is modulated by inputs from submucosal and myenteric neurons, local viscerofugal neurons as well as inputs from spinal sensory afferent neurons [reviewed in (515, 516)]; the influence of the sympathetic nervous system over GI functions is modulated, therefore, in an ongoing manner, by local activity within the intestine. In contrast, sympathetic vasoconstrictor neurons regulate GI blood flow independently of viscerofugal enteric neurons and are regulated instead by descending CNS inputs.

CNS regulation of sympathetic and parasympathetic control of gastrointestinal functions

As mentioned earlier, vagal neurons within the hindbrain receive inputs from several other brainstem and higher CNS nuclei involved in the regulation of autonomic GI functions. The use of retrograde transneuronal viruses has enabled the identification of CNS nuclei that innervate preganglionic neurons involved in the regulation of GI targets, although distinguishing sympathetic from parasympathetic preautonomic pathways has been hampered by the close interaction between afferent projections from both pathways at the level of the brainstem, particularly the NTS. Further difficulties arise in separating innervation to the NTS from that of the DMV due to the close intermingling of dendrites from neurons of both nuclei. Nevertheless, studies in which transsynaptic virus labeling has been carried out in conjunction with selective denervation of sympathetic or parasympathetic afferents has allowed some delineation of parasympathetic versus sympathetic pathways (85,251,408; for similar studies investigating the central innervation of the pancreas).

Spinal Cord

Visceral organs, including the several regions of the GI tract (stomach, small intestine, and proximal large intestine), receive dual innervation from both the sympathetic and parasympathetic nervous systems. As described previously, sympathetic afferent fibers from the GI tract terminate in the thoracic (T1–T13) spinal cord. Several neuroanatomical tracing studies have demonstrated that ascending projections from dorsal horn of the spinal cord project *directly* to several CNS structures involved in the processing of GI autonomic information, including the NTS (spinosolitary tract), the hypothalamus (spinohypothalamic tract), the PB complex (spinoparabrachial tract) as well as the periaqueductal gray (PAG) and amygdala via the spinomesencephalic and spinotelencephalic tracts, respectively

(87,88,99,302,329,330,481). Many of these CNS nuclei also receive parasympathetic sensory information, albeit indirectly via NTS efferent projections; this allows for a considerable degree of consolidation and integration of visceral (and somatic) information at multiple sites within the CNS.

The NTS, however, is the only central nucleus that is the recipient of both *direct* parasympathetic and sympathetic sensory information (Fig. 1). It is widely accepted that nociceptive information is relayed centrally via spinal afferent neurons while visceral reflex and integrative functions are transmitted by vagal afferents. Several lines of evidence, however, indicate that spinal visceral afferents are also activated by low pressure distention and innocuous chemical stimulation and therefore may also relay non-nociceptive information centrally (250,375,398) while vagal afferents also respond to noxious stimulation (490,491). This convergence of vagal and spinal afferent sensory inputs within the NTS allows a significant degree of overlap between the integration and processing of sympathetic and parasympathetic visceral information. As a consequence, vagal afferents are also able to modulate nociceptive processing (248, 387, 397) while spinal afferents can modulate vagal efferent motor control of the upper GI tract (234, 398).

Hindbrain nuclei regulating gastrointestinal functions

Area postrema—The area postrema is a circumventricular area located dorsal to the NTS that was identified as an emetic chemoreceptor trigger zone in the 1940 to 1950s (63, 64, 530). As with other circumventricular organs, the area postrema is highly vascularized with fenestrated capillaries and, as a result, is less isolated from the peripheral circulation by the blood brain barrier than other CNS nuclei (111, 171). Furthermore, the dendrites of area postrema neurons extend towards the basal lamina side of vascular endothelial cells allowing them to receive, and respond to, blood-borne information from the periphery (382). Additionally, the dendrites of NTS and even DMV neurons have been observed to project towards the ependymal layer of the fourth ventricle allowing them to also respond directly to circulating mediators (437). The majority of area postrema neurons are spontaneously active due to the presence of a hyperpolarization-activated cation current [I_H, (442)] and primarily innervate the adjacent NTS but also send projections to the nucleus ambiguus, DMV and parabrachial nucleus (171, 382) (Fig. 1). Area postrema neurons contain receptors for several neurotransmitters, neuromodulators, and immune mediators [reviewed in (127,382)], hence, are ideally situated to allow modification of vagal efferent outflow to the GI tract, including emetic reflexes, in response to circulating factors.

Reticular formation—The reticular formation (or substantia reticulata), named for its mesh-like appearance, is a diffuse network of cells that surrounds the more compact, named nuclear structures of the brainstem. Although more recognized for its role in the integration of cardiovascular and respiratory functions, the reticular formation is also involved in several GI reflexes. Physiological as well as noxious gastric distention has been reported to induce vagal afferent-mediated reflex alterations in blood pressure and heart rate in rats, cats, and pigs (306, 356, 482, 504), effects that may involve the activation of neurons within the reticular formation (338,419). The integration of cardiovascular with GI reflexes within the reticular formation may provide a neuroanatomical basis for clinical findings that

stimulation of gastric mechanoreceptors modulates hemodynamic reflexes, including, for example, decreased coronary blood flow and cardiac contractility following gastric distention (503). The integrative capacity of the reticular formation may also play a role in the co-ordination of several autonomic reflexes required for the generation of vomiting, which is associated with an increase in blood pressure, altered heart rate, and co-ordinated activity of several respiratory muscle groups in addition to the well-recognized modulation of GI and esophageal functions [reviewed in (19)].

Ventrolateral medulla—It has been known for some time that stimulation of abdominal vagal afferents increases arterial blood pressure (114, 184, 351) and that this response is abolished by vagotomy (114). Anatomical and functional studies have demonstrated a robust excitatory input from NTS neurons (the recipient of vagal afferent sensory information) to neurons within the caudal ventrolateral medulla and the rostral ventrolateral medulla (RVLM; premotor sympathoexcitatory neurons). Neurons within the RVLM then project directly to sympathetic preganglionic neurons within the IML column of the spinal cord to regulate vasomotor outflow [reviewed in (208)]. Vagal afferents are activated by a variety of stimuli [mechanical, chemical, and osmotic, for example; reviewed in (52)] and activation of RVLM neurons in response to more physiological stimuli have also been reported, including low intensity (i.e., non-noxious) gastric distention (419) and chemical stimulation, for example, bitter tastants (210). Systemic CCK, in contrast, inhibits the activity of RVLM neurons that regulate sympathetic vasomotor outflow to the splanchnic circulation. In this manner, CCK released from enteroendocrine cells in response to a mixed meal results not only in a vago-vagal reflex relaxation of the stomach (231, 392) but also mediates postprandial blood flow to the guts via a GI vagal-sympathetic vasomotor reflex (428, 521).

The NTS is the first relay network for GI, gustatory, cardiovascular, and respiratory sensory information from the viscera and projections from the NTS to the VLM allow for the integration of autonomic reflexes (Fig. 1). In addition, both the NTS and the VLM also have reciprocal connections with, and convey visceral afferent information to, the central nucleus of the amygdala (CeA) and the PAG. As described in more detail below, neural projections to and from these nuclei are important for the co-ordination of behavioral responses such as learning/memory and fear/anxiety with autonomic homeostatic control (522).

Trigeminal nucleus—While the trigeminal system is involved predominantly with processing sensory inputs from the head and face, neurons within the oral part of the spinal trigeminal nucleus are activated following high frequency/high intensity gastric distention (419). The existence of a nasogastric reflex in humans has been proposed; this reflex involves activation of trigeminal afferent fibers in response to nasal irritation resulting in gastric relaxation and increased acid secretion mediated via vagal efferent nerves (307, 444). Certainly, neuroanatomical studies using anterograde tracers have indicated that the anterior ethmoidal nerve within the nose, a major component of the afferent pathway of the diving reflex, innervates the trigeminal nucleus and NTS (365). The existence of a naso-gastric reflex is still somewhat controversial, however, and the GI symptoms observed following trigeminal stimulation may be the GI effects secondary to activation of the trigeminocardiac reflex (431).

Raphe nuclei—Several lines of evidence have suggested that the medullary raphe nuclei are an important site of vagally mediated modulation of gastric activity (237, 464). Microinjection of TRH into the DVC increases gastric motility and acid secretion in a vagally dependent manner (221, 452, 463, 535). Additionally, activation of neurons within the raphe pallidus, raphe obscurus, or parapyramidal regions induces a vagally dependent increase in gastric acid secretion that is attenuated by pretreatment with DVC microinjection of a TRH antibody (176, 222). TRH has also been shown to excite DMV neurons via direct actions on their neuronal membrane (497). Immunohistochemical studies showed a high density of TRH-immunoreactive fibers within the DVC (236, 310) that were eliminated following transection of the pathway from the medullary raphe nuclei to the DVC (364). Medullary raphe neurons have also been shown to contain and release 5-HT and substance P which have also been implicated in modulation of gastric functions including motility and secretion (273, 464, 476, 477) via actions at DVC neurons (7, 75, 76, 292, 378, 532).

Innervation of the DVC by TRH-containing medullary raphe neurons has been implicated in the increased gastric acid secretion in response to two distinct physiological reflexes. Firstly, the cephalic phase of digestion induces an increase in gastric acid secretion in response to the sight, sound, smell, taste, and swallowing of food; this vagally mediated response was subsequently demonstrated to be blocked by intracisternal application of TRH receptor antisense oligonucleotides [(319); reviewed in (381)]. Secondly, exposure to cold increases gastric motility and acid secretion in a vagally dependent manner, subsequent to activation of raphe pallidus, raphe obscurus and parapyramidal neurons (89, 464). These findings suggests that the medullary raphe nuclei play an important role in the regulation of vagally mediated gastric functions, particularly gastric acid secretion, and this neurocircuitry can be activated by both physiological and pathophysiological conditions.

Midbrain nuclei regulating gastrointestinal functions

Cerebellum and Vestibular System—While the cerebellum is traditionally considered as a subcortical motor center, it is clear that it also plays important roles in several GI-related autonomic functions. Claude Bernard, in 1858, famously described hyperglycemia resulting from cerebellar lesions. The cerebellum also certainly appears to be involved in the nausea and vomiting associated with motion sickness, although this appears to be a modulatory, rather than the principle, role (332). Recent behavioral studies have noted that cerebellar lesions results in altered food intake and decreased body weight in rodents (553).

Cerebellar neurons are activated following gastric distention in both humans (280) and rodents (336). Additionally, neurophysiological experiments have also shown that neurons within the DVC, including both NTS and DMV neurons, receive convergent inputs from the cerebellar or vestibular system and the GI tract (293, 453) (Fig. 1). The cerebellum is able to influence and modulate GI functions by way of indirect inputs to the brainstem; cerebellar neurons innervate the DVC via the vestibular nucleus (cerebellovestibular fibers) as well as from the hypothalamus (cerebellohypothalamic fibers) via the parabrachial and Kölliker-Fuse nucleus [see above; (27, 453)]. Following stimulation of the cerebellum, gastric, and intestinal motility, as well as gastric acid secretion, are modulated by both vagally dependent as well as vagally independent pathways (298, 314).

It appears, therefore, that the cerebellum does more than co-ordinate motor activity, playing an important role in the co-ordination of somato-visceral reflexes including the integration of several GI functions. The role of the cerebellum in the control of food intake as well as its involvement in several other autonomic pathways including cardiovascular, respiratory, emotional and cognitive [reviewed by (553)] suggests a more wide-spread integrative capability.

Parabrachial Complex—The parabrachial nucleus (PBN), within the brachium of the pons, is composed of several subnuclei; the medial PBN is part of the gustatory system while the lateral PBN is part of the visceral sensory system. The medial PBN receives gustatory information from the NTS whereas the lateral PBN, in contrast, receives GI viscerosensory information from both the NTS and the AP (218) (Fig. 1). The PBN, together with the Kölliker-Fuse nucleus, positioned within the ventrolateral extent of the nucleus, forms the parabrachial complex (PB complex). The PB complex integrates the gustatory and GI sensory information received from the NTS together with general visceral information (cardiovascular, respiratory, and nociceptive) received from the NTS and AP plus GI and seomatosensory information from the cerebellum (408). Indeed, studies have demonstrated that PB complex neurons may receive converging inputs from vestibular and visceral vagal afferents (453) and from orosensory and visceral vagal afferents (259) suggesting some potential for integration of afferent information.

PB complex neurons relay this sensory information to a number of structures including the thalamus, insular cortex, central nucleus of the amygdala (CeA) and lateral hypothalamus (172) (Figs. 1 and 2). Neurons of the PB complex also receive reciprocal connections from several of these higher ascending structures, including the cortex, basal forebrain and hypothalamus (337). Descending projection from the PB complex innervate the RVLM as well as the NTS (218) while descending projections from the Kölliker-Fuse nucleus innervate the sympathetic preganglionic column of the spinal cord, the nucleus ambiguus, the NTS and the rostro- and ventrolateral medulla (448). The PB complex, therefore, occupies an important position as an integrative relay between brainstem and forebrain integrative autonomic regulation and provides a neuroanatomical substrate for the involvement and integration of affective and emotional responses to visceral, including GI and gustatory, sensory information (259).

Hypothalamus—The hypothalamus, located rostral to the brainstem, just below the thalamus, is composed of a number of nuclei that regulate a variety of autonomic functions including linking the nervous and endocrine systems via the pituitary gland. With regard to central regulation of GI functions, the paraventricular nucleus of the hypothalamus (PVN) and the arcuate nucleus are of particular importance.

The PVN receives both ascending and descending inputs from structures involved in the autonomic regulation of GI functions including the spinal cord, NTS, PB complex, bed nucleus of the stria terminalis (BNST), CeA [reviewed in (457) (Figs. 1 and 2)]. The PVN itself contains discrete subpopulations of neurons that subserve distinct functions; magnocellular neurons, for example, contain oxytocin (OXY) or vasopressin and release these neurotransmitters into the posterior pituitary gland (i.e., neurohypophysis).

Parvocellular neurons, in contrast, contain hormones, particularly corticotrophin-releasing hormone (CRH; also known as corticotropin-releasing factor, CRF) and OXY and either release these neurohormones into the hypophysial portal system or project to other central nuclei involved in autonomic regulation and control, including the PAG, PB complex, DVC, ventrolateral medulla, and sympathetic preganglionic neurons in the spinal cord (308, 426, 457) (Figs. 1 and 2). Many studies have reported the importance these hypothalamic neuropeptides, particularly in the response of the GI tract to stress. CRF, the prototypical stress neuropeptide, acts as a neurotransmitter as well as a neurohormone involved in HPA axis activation in co-ordinating the autonomic response of the GI tract to stress [reviewed in (450)] and several lines of evidence suggest that altered central and peripheral CRF signaling plays a role in the stress-induced development and maintenance of functional bowel disorders [(460, 462); see below]. *In vivo* and *in vitro* studies have shown that CRF activates DMV neurons (directly as well as indirectly via actions to increase glutamatergic synaptic inputs) and decreases gastric motility via activation of the vagally dependent NANC pathway (224, 291). Indeed, central application of a CRF antagonist has been shown to prevent the postoperative ileus observed following abdominal surgery, suggesting involvement of a gastro-inhibitory CRF-dependent pathway.

In contrast to its effects to inhibit gastric motility and emptying, CRF acts centrally to accelerate colonic motility and transit [reviewed in (450)] via activation of both vagal and sympathetic pathways innervating the proximal and distal colon (245, 501). As discussed below, stress causes the activation of CRF-containing neurons within Barrington's Nucleus and PVN that project to the LC (202, 289, 340, 342) that not only increases colonic transit but also increases arousal and anxiety-like behaviors which may be of importance in the pathophysiology of functional bowel disorders such as irritable bowel syndrome (IBS) associated with comorbid anxiety and depression (335, 461, 505).

In contrast to the prostress actions of CRF, OXY is the prototypical antistress neuropeptide. The PVN is the sole source of OXY-innervation to the DVC and OXY-containing axons and fibers have been shown to form close appositions to NTS neurons as well as gastric-projecting DMV neurons (304, 376). Electrophysiological studies support the role of OXY to modulate vagally mediated GI functions; OXY excites DMV neurons via a cAMP-sensitive current (6, 229, 385, 386) and increases glutamate release from vagal afferent terminals (376). OXY is released from the PVN following meal ingestion and acts within the DVC to stimulate gastric acid secretion and decrease gastric motility via a vagally dependent pathway (229). In fact, these OXY-releasing inputs to the DVC are tonically active since intracerebroventricular application of OXY antagonists increases baseline gastric motility (161). Furthermore, electrical stimulation of the PVN induces a vagally dependent decrease in gastric motility and increase in gastric acid secretion (404), actions that are blocked by DVC application of an OXY antagonist and mimicked by microinjection of an OXY agonist. As an antistress peptide, hypothalamic OXY plays an important role in the recovery of GI functions following adaptation to stress [(25, 26, 86, 548); see below)].

The arcuate nucleus (Arc) of the hypothalamus, located adjacent to the third ventricle in close apposition to the median eminence and the pituitary gland is connected to both via neuronal and humoral connections. The Arc is also a circumventricular organ (111,171) and

Arc neurons have been shown to modulate their activity in response to several circulating neuropeptides and neurohormones which regulate GI functions (57). The Arc also has extensive afferent and efferent projections to several brain regions underscoring its important role in the modulation and regulation of a variety of autonomic homeostatic functions. With respect to its involvement in the regulation of GI functions, the Arc receives afferent inputs from other hypothalamic areas as well as from the LC, NTS, reticular formation, the BNST, and PVN (106, 134). In turn, Arc neurons send projections to other hypothalamic nuclei as well as to the limbic system, the thalamus and the brainstem, including the PAG and DVC, highlighting the role of this nucleus in the integration of endocrine and behavioral aspects of autonomic GI regulation (106).

In addition to its role in the modulation of feeding and satiety, stimulation of Arc has also been demonstrated to increase colonic motility and transit (471) and decrease gastric acid secretion (470). The promotility colonic effects were antagonized by application of CRF antagonists to the PVN while the effects on gastric acid secretion were blocked by a combination of CRF and NPY Y1 receptor antagonists, suggesting that an Arc-PVN neurocircuit may also regulate GI functions via vagally dependent efferent effects (469–471).

Barrington's Nucleus—Barrington's nucleus, located within the dorsolateral pontine tegmentum, often known as the pontine micturition center, is involved in the supraspinal regulation of both bladder and colonic functions (37,370). Transsynaptic tracing studies have demonstrated that an individual neuron within Barrington's nucleus may innervate both the bladder and the colon, suggesting coregulation of viscera through projections to preganglionic parasympathetic neurons in the lumbosacral spinal cord (417). Consistent with this neuroanatomical evidence, functional studies have shown that most Barrington's nucleus neurons respond to bladder distention with an increase in activity; approximately half of these neurons also respond to colonic distention (418). Furthermore stimulation of Barrington's nucleus produces increases in colonic pressure via activation of lumbosacral parasympathetic preganglionic neurons (370). This suggests that information from the bladder and colon converges onto Barrington's nucleus neurons which, in turn, can influence the parasympathetic outflow to both organs (418).

A significant proportion of Barrington's neurons are immunoreactive for CRF (507), indeed, CRF-immunoreactivity within this pontine region has been suggested to be a definitive marker of Barrington's nucleus (506). Additionally, the majority of colon-responsive Barrington's neurons are CRF-immunopositive (418). CRF-containing neurons within Barrington's nucleus also project to the lateral DMV (507), an area known to provide parasympathetic innervation to the proximal colon (11, 49, 74), to the spinal cord and to the LC (370). Several studies in many CNS areas have provided evidence for the important role of CRF in the co-ordinated physical and homeostatic response to anxiety and stress [reviewed in (28)]. Indeed, CRF levels within Barrington's nucleus increase in response to both acute and chronic stress (243, 244) which may be of importance in stress and stress-related colonic dysfunction (454, 462, 505). While Barrington's nucleus has been considered to be involved almost exclusively with the control of parasympathetic functions, neuronal tracing studies have also demonstrated that neurons within Barrington's nucleus innervate

sympathetic preganglionic neurons in the thoracic spinal cord, either directly or indirectly, suggesting a role in the integration of both sympathetic and parasympathetic autonomic functions (95).

Several neuroanatomical and functional studies have investigated the projections from the lumbosacral spinal cord to Barrington's nucleus (139, 417, 506). In addition to these visceral sensory afferents, neurons within Barrington's nucleus are also the recipients of inputs from a diverse range of brainstem, midbrain, and forebrain structures. Retrograde tracing studies have demonstrated that the greatest density of projections to Barrington's nucleus arise from the PAG area, the lateral hypothalamus (LH) and the medial preoptic nucleus (506). Anterograde labeling studies further suggested that the PAG and LH neurons innervating Barrington's nucleus target CRF neurons specifically (506). Retrogradely labeled neurons were also identified in the NTS, the PB complex, the dorsal and medial raphe nuclei, zone incerta, tuberomammillary and premammillary nuclei, BNST, dorsal, ventromedial, and PVN hypothalamic areas as well as motor, insular and infralimbic cortices (506). Such a variety of projections to and from Barrington's nucleus, which includes connections with neurons at all supraspinal levels (brainstem, midbrain, pons, and forebrain) suggests involvement in a variety of integrative processes and may provide a neuroanatomical basis for assimilation of GI functions with emotional and cognitive behaviors.

Periaqueductal gray—The PAG refers to an area of the midbrain surrounding the cerebral aqueduct extending caudally from the dorsal tegmental nucleus to the most rostral level of the third nucleus at the level of the posterior commissure. The PAG contains prominent longitudinally arranged fiber systems connecting the forebrain with brainstem autonomic neurocircuits. In addition to its role in autonomic processing, the PAG is important in the regulation and processing of fear and anxiety, in vocalization and in the ascending transfer, as well as descending modulation, of nociceptive information [reviewed in (42)].

Neuroanatomical tracing studies have shown that the PAG receives a dense innervation of predominately catecholaminergic inputs from NTS and rostral ventrolateral reticular nucleus (RVL; involved in the integration of cardiovascular and respiratory reflexes) as well as inputs from neurons within lamina I and, to a lesser extent, lamina V of the spinal cord (Fig. 1) (219,263,276,458). Thus, both parasympathetic and sympathetic sensory information from the GI tract can be relayed to the PAG. Together with the inputs from the hypothalamus (96, 475), and inputs from forebrain regions including the prefrontal and cingulate cortex and, pre- and infra-limbic areas (Fig. 2) (160, 163, 240, 409), this allows for the PAG to integrate and modulate autonomic and emotional information from all supraspinal levels. The PAG provides reciprocal connections back to many of these regions, including the central nucleus of the amygdala (CeA), the hypothalamus, and spinal cord (295, 396, 409, 410) as well as projections to the raphe magnus, the LC and ventrolateral medulla (153, 509). Efferent projections to PB complex (272) potentially acts as filter system that depends on behavioral state to modulate ascending nociceptive or visceral information through the PB complex to forebrain areas, while efferent projections to the hypothalamus provides an additional, and significant, means by which sympathetic and parasympathetic autonomic homeostatic functions can be integrated.

Noxious gastric (104) and colonic (320, 492) stimulation activates supraspinal CNS regions, including PAG, that are involved in somatic pain processing suggestive either of a degree of overlap of nociceptive processing, or of a common central pain mechanism. In turn, PAG neurons activated by noxious stimulation of the GI tract project to the PVN (141). The critical role that the PAG plays in descending pain inhibition was confirmed by studies demonstrating that stimulation of the PAG induces profound analgesia (42, 401). While the mechanism is not completely understood, PAG stimulation appears to result in inhibition of dorsal horn nociceptive neurons (97, 374). The relatively sparse direct innervation of the spinal cord by PAG neurons (315) led to the suggestion that the analgesia resulting from PAG stimulation occurred indirectly via the medulla, particularly the nucleus raphe magnus (5, 396) although this medullary relay nuclei may not be solely responsible for the descending antinociceptive pathway activated from the PAG (179, 423).

Locus coeruleus—The LC (A6 noradrenergic region), located within the rostral pons at the lateral floor of the fourth ventricle, is the brain's predominant source of noradrenergic innervation. LC neurons are spontaneously active (537); the activity and firing rate of neurons within the LC increase in response to sensory, autonomic and painful stimulation and decrease during sleep, suggesting the involvement of this nucleus in the maintenance of attention and arousal [reviewed in (17, 165)]. Historically, the identification of inputs to the LC has been controversial but more recent neuroanatomical tracing techniques have identified several inputs from autonomic-related nuclei (Fig. 2); inputs from the NTS provide a means by which vagal sensory information can be relayed to the LC (510). Inputs from the PVN [(399); see above], Barrington's nucleus [(416, 454); see above], the PB complex [(309); see above], and PAG [(309); see above] provide a means by which vagal and spinal GI afferent information converge and can be integrated. Inputs from the BNST, central CeA, and from the prefrontal cortex (16, 309, 508) provide a means by which the autonomic components of emotional responses can be integrated with higher cognitive inputs (reviewed in (165). Both the location of the LC, in close proximity to the fourth ventricle and several large blood vessels, and the extensive dendritic projections, including toward the ependymal layer of the fourth ventricle, has led to speculation that they may be responsive to circulating neuroactive agents although this remains to be confirmed (201, 455).

The LC has extensive efferent connections including reciprocal connections with several of these areas mentioned above involved in autonomic GI regulation such as the brainstem (NTS; trigeminal) and hypothalamus, particularly the parvocellular region of the PVN (119,269,429). Efferent projections from the LC to the spinal cord have been found within the ventral columns, intermediate gray and ventral half of the dorsal column (4, 110, 162), although there may be regional and species variations. In the rat, for example, the LC has been estimated to provide 70% to 90% of noradrenergic inputs to some (but not all) levels of the spinal cord (260) and was found to be the sole source of noradrenergic inputs to the ventral horn (110). In contrast, Commissiong et al. (109) found that the LC does not innervate the dorsal commissural nucleus of the thoracic spinal cord and was, therefore, unlikely to influence the activity of sympathetic preganglionic neurons innervating the upper GI tract. Significant species differences appear to exist, however; studies by Westlund and

Coulter in the monkey demonstrated that, in addition to projections to the sacral spinal cord, LC innervates the DVC and nucleus ambiguus suggesting an involvement in descending modulation of vagal parasympathetic regulation (534). Efferent projections from the LC to the cortex as well as projections to the cerebellum, thalamic relay network and amygdala provide a neuroanatomical basis for the involvement of the LC in attention and arousal [reviewed in (165)]. Multiple experimental approaches have demonstrated that NE exerts a profound influence over arousal and behavioral states; LC activity, in particular, acts as a gate on several modalities of sensory processing. By effectively increasing the signal to noise ratio of sensory inputs, the LC assists in enhancing and "tuning" the response to a specific stimulus [reviewed in (17, 427)].

Both immunohistochemical and electrophysiological studies have demonstrated that distention of the stomach or colon activates LC neurons in a pressure-dependent manner (152, 320, 416, 419). The colonic-distention induced increase in LC neuronal activity appears dependent upon CRF released from Barrington's nucleus (507), although other nuclei (PVN, CeA, and BNST, in particular) innervate the LC with CRF-containing fibers (399). Microinjection of CRF into the LC stimulates colonic motility and accelerates colonic transit significantly but has no effect upon gastric motility or emptying (341, 462). Despite having no effect on gastric motility or emptying, microinjection of CRF into the LC inhibits gastric acid secretion; vagotomy had no effect upon this action of CRF suggesting it involves activation of a spinal pathway (342).

Interestingly, abdominal surgery activates LC neurons [in addition to activating neurons within the PVN, NTS, and supraoptic nucleus; (60)]. While this activation also involves CRF, it does not appear to involve a vagal pathway but rather activates a splanchnic afferent-spinosolitary tract-NTS-PVN-LC pathway that may be involved in the gastric ileus observed following abdominal surgery (35, 60). Stress also increases CRF levels within Barrington's nucleus and alters CRF neurotransmission within the LC; acute stress attenuates LC neuronal response to CRF but repeated stress results in a sensitization of LC neurons (121) which may play a role in the well-described stress-induced alterations in GI functions (460, 505, 508).

Stress also activates the hypothalamic-pituitary-adrenal (HPA) axis resulting in the release of glucocorticoids from the adrenal gland. In addition to exerting multiple effects throughout the periphery, corticosteroids also exert profound effects on several CNS nuclei [reviewed in (220, 347)], including (i) activation of the CeA, BNST, PVN (regions which provide innervation to the LC) as well as the LC itself, (ii) the upregulation of CRF or CRF mRNA in CeA, BNST, PVN, and (iii) altered expression profiles of mineralocorticoid and glucocorticoid receptors in CeA, BNST, and LC. Together, these provide potential a neuroanatomical basis for the well-known effects of stress to induce colonic motor dysfunction and increase colonic pain sensitivity (120,121,294,485,486,520).

Cellular plasticity of LC neurons, particularly dependence and withdrawal in response to opioid drugs has been well described. Acutely, opioids inhibit LC neuronal activity (decreased adenylate cyclase activity as a consequence of increased potassium conductance) (493, 538, 539). In contrast, chronic opioid administration induces the development of

opioid tolerance and dependence via upregulation of the cAMP-CREB pathway resulting in increased neuronal activity and firing rate [reviewed in (326)]. Opioid drug use, therefore, may result in bowel dysfunction via alterations in LC neuronal activity irrespective of actions at peripheral opioid receptors within the GI tract (474).

Forebrain nuclei regulating gastrointestinal functions

Central nucleus of the amygdala—The central CeA, rather than being a single anatomical or functional structure, is a relatively large, heterogeneous complex located within the anteromedial temporal lobe and is involved in learning and memory as well as the integration of aversive and emotional stimuli with learning and memory as well as autonomic, including GI, functions [reviewed in (217, 456)]. As an important structure within the limbic system, the CeA facilitates the processing of autonomic and emotional sensory information and appears to play a prominent role in the development of anxiety and stress-related GI disorders [reviewed in (345)].

The CeA receives inputs from structures at all supraspinal levels including the brainstem [NTS and ventrolateral medulla; (353,362,403)] the midbrain [PB complex, hypothalamus, and PAG; (47, 362, 425, 436)] and forebrain [insular cortex and thalamus; (285,424,542); (Fig. 2)]. In turn, the CeA sends reciprocal efferent connections to many of these nuclei including descending projections to several areas involved in autonomic regulation of GI functions such as the LC, Barrington's nucleus, hypothalamus, PAG, NTS, DMV, and ventrolateral medulla (98, 196, 468, 505, 511, 517). The afferent and efferent connections of the CeA permit the integration and modulation both ascending and descending information allowing it to function as a major center for the altered perception of visceral and somatic information.

Several studies have demonstrated that the CeA modulates the effects of stress on the development of gastric pathology. Stimulation of the amygdala increases gastric acid secretion (216, 223, 266) while lesions of the amygdala attenuate the formation of stress-induced gastric ulcers (214); these effects were abolished by vagotomy (223, 266) illustrating the role descending pathways from the amygdala exert upon the modulation of vagal efferent activity. Indeed, studies have suggested that the integrity of the CeA is important for the maintenance and integrity of gastric mucosa (343). Multi-unit electrophysiological studies of CeA neurons have shown that the firing patterns and response profiles of neurons from rats susceptible to the development of stress-induced ulcers differs from those of resistant rats, suggesting that variations in emotional state influences the GI response to stressful events and that the behavior of CeA neurons plays a significant role in either adaptation to stress (215) or in the perception of visceral stimulation (345).

While the role of the amygdala to modulate gastric motility has not been studied to the same degree, nevertheless it has been known for some time that, in anesthetized animals, stimulation of the CeA alters gastric pressure (increased or decreased depending on the medial-lateral location of the stimulating electrode) in a vagally dependent manner (157, 303, 311). The role of the amygdala in regulation and modulation of GI functions is not restricted to the stomach, however. As a major efferent nucleus involved in the generation of fear and anxiety behaviors as well as the acquisition of emotional memories, the CeA plays a

prominent role in linking stress and anxiety with the development of GI, particularly colonic, hypersensitivity (345).

Indeed, stimulation of the CeA increases anxiety-like behaviors and augments stress-induced responses via actions, at least in part, that activate the HPA axis. In contrast, lesions of the CeA decrease anxiety-like behaviors, decrease CRF mRNA expression and CRF levels within the hypothalamus and decrease the stress-induce release of ACTH and corticosteroids (91, 519); reviewed in (133). Functional magnetic resonance imaging (fMRI) and positron emission tomography techniques have demonstrated that patients exhibiting GI hypersensitivity show altered processing of visceral stimulation and increased activation of several CNS regions including the amygdala (322, 323) while rodent studies have shown an increased neuronal activation in CeA following colorectal distention (283, 533). Alteration of amygdala activity is also known to modulate the response to visceral stimulation; activation of glucocorticoid or mineralocorticoid receptors, for example, by exposure of the amygdala to corticosterone, increases the response to colorectal distention, supporting the hypothesis that the amygdala plays an important role in the perception and processing of visceral sensations (198, 345, 346). Similarly, central administration of the prototypical stress neuropeptide CRF is well-known to increase colonic activity; microinjection of CRF antagonists into the CeA attenuates these stress-induced effects. Furthermore, stress-susceptible species of rodents have been found to have increased levels of CRF within the CeA (206, 439) and CeA CRF levels are also increased in animal models of colonic hypersensitivity (199, 380). In addition to increasing anxiety- and stress-related behaviors, microinjection of corticosterone into the amygdala increases CRF levels (485); these actions are also attenuated by CRF antagonists (91). These, and other lines of evidence, have led to the suggestion that the sensitivity of the CeA to corticosterone may underlie the correlation between the stress and GI hypersensitivity observed in many IBS patients [reviewed in (345)].

Bed Nucleus of the Stria Terminalis—The 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 (166). As with the amygdala, the BNST receives afferent inputs from nuclei at all supraspinal levels including the brainstem (NTS, ventrolateral medulla and PB complex; (441), midbrain [hypothalamus, PAG (8, 441)], and forebrain nuclei [cortex, rostral forebrain structures, and thalamus (424, 441, 542)] as well as the CeA itself (271, 383); (Fig. 2). The BNST projects to several areas involved in autonomic homeostatic regulation of GI functions including the NTS, DMV, PAG, hypothalamus, LC, and PB complex (46, 196, 232). As a result, the BNST is well placed to integrate physiological and behavioral responses.

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 (213, 343). The majority of BNST neurons display a GABAergic phenotype, 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 (115). Although some BNST inputs to the PVN are CRF-immunoreactive, anatomical studies indicate that the majority of the BNST inputs to the PVN are GABAergic (379), suggesting (i) that the BNST exerts a predominantly inhibitory influence over the HPA axis activity and (ii) that activation of the HPA axis may arise either from activation of CRF-containing BNST inputs or disinhibition of GABA-containing BNST 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 (105).

The BNST is volumetrically and neurochemically sexually dimorphic in both humans and rodents (9, 225), particularly with respect to CRF and vasopressin-immunoreactivity (331, 334). Furthermore, both estrogen and androgen receptors are expressed within the BNST (445); activation of androgen receptors appears to enhance stress-induced PVN activation and may enhance HPA axis activation (55, 209). Further, the level of CRF within the BNST has been shown to fluctuate in concert with the estrous cycle (360) providing a neurophysiological basis for the differential influence of gender and sex hormones in the modulation of BNST, hence, HPA axis, activity.

Cortex—In addition to modulating GI functions via descending connections via the hypothalamus and the amygdala (see above), the cortex can modulate GI functions via direct descending connections from the infralimbic and prelimbic cortex to the dorsal vagal complex (363, 443, 472, 473, 511, 512). Stimulation of the infralimbic cortex induces gastric relaxation and decreases both gastric motility and tone in a vagally dependent manner (241,366,542). Several recent studies have highlighted the effects that cortical influences, including affect, motivation, and memory, exert over GI functions and the consequences that disturbances within this system exerts upon a variety of functional and inflammatory GI disorders (61,324).

Central regulation and modulation of gastrointestinal reflexes

The discussions above regarding the central modulation of GI functions have been written primarily from the point of “normal” or “basal” regulation. Increasing evidence indicates, however, that central regulation of GI functions does not occur in a static or inflexible manner but, rather, exhibits a remarkable degree of plasticity and adaptation.

During the intermeal interval, mammalian GI motor activity oscillates between periods of quiescence (Phase I) and different levels of activity (irregular, Phase II, or caudally migrating bursts of contractions, Phase III). During these phases, the proximal stomach experiences a (vagally mediated) tonic contraction, and the subsequent alternate periods of quiescence or activity occur in synchrony with the motor activity in the antrum and proximal small intestine. Meal ingestion and food transit from the stomach to the upper small intestine disrupt these cyclic patterns of activity and induce long-lasting relaxation of the proximal stomach [reviewed in (135)]. Many different types of vago-vagal reflexes (esophago-gastric, gastro-gastric, duodeno-gastric, and intestino-intestinal, for example) contribute to the CNS

control of this gastric relaxation and it is not our intention to provide details of them all of them but, rather, we refer the reader to the numerous manuscripts and reviews that have dealt specifically with these functions [see, among others (132, 154, 498)]. Instead, we describe a few select GI reflexes briefly, as examples of feedback mechanisms that control and regulate meal transit through the GI tract to optimize digestive processes, and the modulation of these reflexes during pathophysiological conditions.

Functional Gastrointestinal Disorders and the Receptive Relaxation (or Esophago-Gastric) Reflex

First described by Walter Cannon in 1911 (94) reflex gastric accommodation to a meal is achieved via relaxation of the proximal stomach, allowing ingested food to be transported into the stomach without an accompanying increase in intragastric pressure. This reflex is mediated entirely by the vagus nerve (411); stimulation of low threshold mechanosensitive esophageal vagal afferents results in proximal gastric relaxation via either inhibition/withdrawal of tonic cholinergic vagal efferent pathways or activation of inhibitory NANC pathways [reviewed in (499)].

Functional GI motility disorders, including functional dyspepsia [FD; defined by the Rome III panel as “the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms” (466)], are frequently accompanied by symptoms such as impaired gastric emptying, reduced gastric compliance, early satiety and weight loss (93, 258, 465, 466, 479). While the pathophysiological mechanisms involved in the development of FD have not been elucidated completely, several studies suggest impairment of the vagal sensory-motor reflex loop connecting the GI tract and the brainstem. Almost 50% of FD patients have disturbed vagal efferent functions and abnormal intragastric meal distribution with preferential accumulation of food in the distal, rather than the proximal, stomach (233,500), suggesting that proximal gastric accommodation is abnormal. Stress-related alterations in gastric motility, along with food ingestion, are well-recognized as being among the main pathophysiological mechanisms involved in the generation of dyspeptic symptoms, and the majority of FD patients associate stressful life events with the initiation or exacerbation of symptoms (180, 465, 479, 514). Patients with FD exhibit gastric dysmotility following stress; anger, for example, inhibits gastric motility in FD patients but not in healthy volunteers. In healthy individuals, however, acute stress delays gastric emptying, supporting the idea of a vagal involvement in dyspeptic symptoms, while chronic stress results in symptoms consistent with the diagnosis of FD (92).

As described above, stress activates neurons within several CNS nuclei, including CRF containing neurons within the PVN, resulting in the release of CRF into brainstem nuclei including the DVC (28,41,296,462). Activation of brainstem CRF receptors decreases gastric motility and inhibits gastric emptying while stimulating colonic motility (460). When administered intracisternally, CRF shifts the motility of the duodenum from that of a fasted pattern towards that of a fed pattern with irregular contractions; in contrast, when administered to a fed animal, CRF maintains the fed pattern but reduces the amplitude of the

antrum motility waves. These effects of CRF on gastric motility suggests its involvement in either the generation or the maintenance of stress-induced gastric dysmotility (177, 289, 291, 462). Application of CRF antagonists to the CNS does not alter basal gastric motility or vagal efferent output, suggesting that CRF pathways are not active tonically; the same antagonists, however, prevent stress-induced gastroinhibition (psychological, visceral, or chemical) (460). CRF receptors are positively coupled to adenylate cyclase and their activation increases intracellular cAMP levels (194). As described earlier, cAMP levels regulates the ability of GABAergic inputs onto gastric projecting DMV neurons to be modulated, hence controls vagal efferent outflow to the upper GI tract [reviewed in (78, 81)]. Stress, therefore, alters the tonic inhibitory input onto vagal efferent motoneurons, thus regulates their firing rate and vagal efferent outflow (Browning and Travagli, unpublished observations).

Acute stress may be best considered as inducing a stereotypical and protective homeostatic adaptation to an internal or external threat. This results in modulation of neural pathways in a time-limited adaptive manner. In this regard, we have demonstrated previously that the activation of the cAMP-PKA pathway (such as following CRF exposure) modulates GABAergic synaptic transmission to gastric projecting DMV neurons for approximately 30 to 60 min before returning to prestimulation levels (73, 80). Thus, the functional GI outcomes of acute exposure to CRF are relatively restricted and do not exacerbate the inhibitory gastric actions of the tonically active oxytocinergic pathway, hence, do not result in a prolonged, and potentially damaging, decrease in gastric functions.

In contrast to acute stress, chronic or prolonged stress presents a more serious challenge to homeostatic adaptive mechanisms and the inability to adapt to ongoing internal or external threats frequently results in GI dysfunction. While acute exposure to stress-related neuropeptides such as CRF results may modulate brainstem vagal neurocircuitry for a relatively short period of time, it is tempting to speculate that chronic exposure to stress results in a long-term, or even permanent, alteration in vagal neurocircuitry. Studies in rats have demonstrated adaptation in the hypothalamic corticotropinergic and oxytocinergic system in response to chronic homotypic stress whereas rats exposed to heterotypic stress fail to adapt (24–26, 86, 547). Such a potential dichotomy in neural rewiring presents a means by which adaptation to stress may be investigated, which may be of importance in understanding why some humans, but not others, show GI dysfunctions in response to ongoing stressful conditions.

Obesity and the Ileal Brake Reflex

As described in detail by Maljaars (313), the presence of unabsorbed or semi-digested fat in the ileum slows gastric emptying and the passage of ingested material through the small intestine, helping to prevent nutrient overload and increasing contact time with the absorptive intestinal epithelium (1, 235, 313, 394, 449). While this reflex was initially thought of as being operative in the diseased gut (i.e., activated only during malabsorbtion (449), later studies have shown that nutrients may reach the distal small intestine even under normal conditions, and re-establish the motility from the fed to the fasted pattern (264, 297).

While the precise mechanism underlying the ileal brake mechanism is still somewhat subject to debate, it appears to involve peptide YY (PYY) and GLP-1 release mainly from enteroendocrine L cells in the ileum and colon following a meal (159). Their release, however, occurs before nutrients have reached the lower gut, indicating a neural (including vagal)-mediated mechanism of release (1).

In addition to its prominent actions to induce insulin release from pancreatic β-cells (143, 144, 478), GLP-1 also has major effects at the level of the CNS, penetrating the blood brain barrier *via* simple diffusion (261). GLP-1 excites vagal afferent fibers and neurons (174,349,350), resulting in an activation of central vagal neurons and neurocircuitry (34,529). It is also important to note, however, that GLP-1 is also produced in preproglucagon neurons of the NTS and are also involved in the regulation of autonomic homoestatic functions [reviewed in (489)]. The exact contribution of peripheral versus central GLP-1 in the vagally dependent central regulation of GI functions remains to be elucidated fully. When administered centrally, GLP-1 acts via vagally dependent pathways to induce the release of insulin, decrease food intake, and delay gastric emptying as well as being involved in interoceptive stress (21, 143, 173, 230, 277, 405, 502, 513). GLP-1 receptors are seven transmembrane (7TM) proteins positively coupled to adenylate cyclase, activation of which increases intracellular cAMP levels and calcium concentration (325); as described above for other neuropeptides positively coupled to adenylate cyclase, activation of GLP-1 receptors would, therefore, be expected to alter the “state of activation” of inhibitory vagal neurocircuits, hence, modulate the activity and firing rate of vagal efferent motoneurons.

Once cleaved by dipeptidyl peptidase IV (DPP-IV), PYY 3–36 works preferentially on Y2 receptors (235); the presence of Y2 receptors on vagal afferent terminals suggests the involvement of a paracrine mechanism of action to induce gastric relaxation, while their location on hypothalamic neurons appears responsible for its anorexigenic effects. A CNS transport system exists, however, and peripherally injected peptide YY ([^{125}I]PYY3–36) and pancreatic polypeptide ([^{125}I]hPP) is transported into the CNS, particularly to the dorsal vagal complex (146, 352). Certainly, pancreatic polypeptide binding sites (Y1–Y5) have been identified within the DVC (312), and both NPY and PYY modulate the activity of vagal neurocircuits (33, 58, 77, 80).

Several studies have shown that the behavior, activity and responsiveness of vagal afferent neurons and fibers are altered by diet and obesity. The ability of GI neurohormones such as GLP-1 and CCK to activate vagal afferents and decrease feeding is attenuated in diet-induced obese animal models and humans (112, 113, 126, 142, 145, 299, 536) and exposure to a high fat diet alters the profile of neurotransmitter/neuromodulator receptors on vagal afferent neurons (131, 369). While little attention has been paid to the effects of diet or obesity on the properties of central neurons, a recent study demonstrated that the responsiveness of vagal motoneurons was also decreased in diet-induced obese rodents (71). This reduced responsiveness may contribute to diminished vagal signaling and attenuated vago-vagal reflex control of GI functions after exposure to a high fat diet and may contribute to the altered gastric motility and emptying observed in obese subjects (299).

Diabetes and Gastrointestinal Reflexes

Effective glucose sensing is of vital importance of the regulation and integration of a variety of physiological functions, including the optimal regulation of glycemic levels. Glucose levels fluctuate dramatically in response to food ingestion and a variety of autonomic reflexes are engaged to regulate gastric motility and emptying, in part to stabilize excessive fluctuations. An increase in plasma glucose levels decreases gastric motility and emptying which, in turn, delays the entry of food into the small intestine thus postponing further glucose absorption and preventing prolonged, and potentially damaging, increases in glycemic levels. Hypoglycemia, in contrast, increases gastric motility to accelerate nutrient delivery to the small intestine.

Within the intestine, glucose modulates the activity of enteric neurons directly (301,430,531) as well as modulating their response to GI neurohormones such as CCK and 5-HT (413). The principle action of glucose to modulate GI motility and gastric emptying, however, occurs via paracrine mechanisms of action. Intraluminal glucose induces the release of neurohormones, particularly 5-HT and GLP-1, from enteroendocrine cells. These released neurohormones activate receptors present on vagal afferent terminals and the resulting excitatory signal is relayed centrally (388–390, 523, 554). As described earlier, the central terminals of vagal afferent neurons use predominantly glutamate as their neurotransmitter hence their activation induces the excitation of second order NTS neurons within the brainstem. The subsequent vagal efferent motor response induces gastric relaxation and decreases motility thereby delaying gastric emptying (440, 552, 554, 555).

Once absorbed from the intestine, however, glucose enters the bloodstream where it continues to modulate GI functions via actions on vagal neurocircuits. Intravenous glucose has been shown to modulate the excitation of vagal afferent fibers to intestinal glucose suggesting that circulating glucose is able to modulate neuronal activity directly (327, 328). Despite the relatively tough capsule (nodose ganglion) surrounding vagal afferent neurons, they are appear accessible to circulating factors (278, 279). While glucose is a universal fuel for neurons, some neurons, particularly within the brainstem and hypothalamus, possess the additional ability to use variations in extracellular glucose levels to modulate their excitability (2, 148, 290). A subpopulation of vagal afferent sensory neurons also possess this ability; vagal afferent neurons innervating the stomach are more likely to exhibit excitatory responses to elevations in glucose while neurons innervating the portal vein are more likely to be inhibited suggesting that the effects of glucose on vagal sensory neurons are specialized as per the sensory information they transmit (193). As in other neurons excited by elevations in glucose levels, this appears to involve the closure of an ATP-sensitive potassium channel (30, 487, 488). The mechanism by which an elevation in glucose level inhibits vagal afferent neurons is not fully characterized although it may involve an ATP-insensitive potassium channel (193).

In addition to its direct actions to modulate vagal sensory neuronal activity, glucose also acts indirectly via modulation of neurotransmitter receptor density on the neuronal surface. In particular, an increase in extracellular glucose levels results in the trafficking of 5-HT3 receptors to the surface of GI vagal afferent neurons whereas a decrease in extracellular

glucose results in their internalization (23). The physiological outcome of this glucose-induced trafficking of receptors is an increase or decrease in 5-HT-mediated inward current in response to an increase or decrease in extracellular glucose, respectively (23). This suggests that, in addition to inducing the release of 5-HT from enterochromaffin cells (170, 391), glucose may also increase the ability of vagal sensory neurons to respond to the released 5-HT, amplifying and prolonging the sensory signal. It appears, therefore, that the physiological responsiveness of vagal sensory neurons is altered by nutritional status (feeding, fasting, glucose level, etc.,) implying that the regulation, modulation, and outcome of GI vagal reflex activation may be dependent upon ongoing homeostatic demands.

Glucose also acts centrally to modulate the release of neurotransmitter from vagal afferent terminals (527). As with vagal sensory somata, glucose induces the trafficking of 5-HT3 receptors to the membrane of vagal sensory terminals, the tonic activation of which increases glutamate release onto NTS neurons (528). Earlier studies have also shown that glucose is able to modulate the activity of brainstem neurons; hepatic vagal afferent fibers that were inhibited by an increase in glucose levels, for example, innervate NTS neurons that are also inhibited by local application of glucose (3), whereas other NTS neurons are excited by an increase in glucose levels (2, 124, 125, 543, 544). As with other central and peripheral neurons, this increase in neuronal activity in response to elevated glucose concentrations appears to involve closure of ATP-sensitive potassium channels (29, 30, 125, 147); the mechanism responsible for the glucose-induced inhibition in neuronal activity remains to be elucidated although modulation of chloride conductances may be involved (30). The effects of glucose to modulate DMV neuronal activity is more contentions, however; a subpopulation of DMV neurons that project via the anterior gastric branch have been shown to modulate their activity in response to glucose levels (2, 268) and ATP-sensitive potassium channels have been identified on DMV neurons (30, 488). Other studies, in contrast, have failed to identify any direct effects of glucose on DMV neurons but, rather, demonstrated indirect effects via modulation of synaptic inputs, particularly GABAergic inputs originating likely from NTS neurons (158).

Since GI motility and emptying are modulated by, and dependent upon, physiological alterations in blood glucose levels (393), it is unsurprising that pathophysiological alterations in glucose levels induce profound GI dysfunction. Gastric hyperactivity has been observed in some rodent models of hyperglycemia and in some diabetic patients, whereas diabetic gastroparesis, defined as delayed gastric emptying accompanied by other upper GI symptoms including early satiety, nausea, fullness, bloating and abdominal pain, has been observed in others (100, 238, 435). While insulin certainly modulates the activity of central vagal motoneurons and alters vagally mediated gastric motility (56, 274), the finding that both Type 1 and Type 2 diabetic patients experience gastroparesis suggests that the hyperglycemia and/or disregulated glycemic control *per se*, plays an important role in the development of symptoms. Hyperglycemia and/or diabetes may alter GI functions via actions at multiple sites, both peripheral and central. Within the enteric nervous system itself, a loss of both enteric neurons and ICC have been reported (101, 136, 246, 358, 359), which may contribute to the observed disordered motility patterns and decreases NANC-mediated relaxation (254, 545). Furthermore enteroendocrine signaling is also disrupted in diabetes (286) as is expression and function of glucose transporters (53, 54, 149, 344).

Centrally, the functioning of both sensory and motor vagal fibers is compromised in diabetes (287, 288, 395, 541) and recent evidence suggests that there is also impaired sensitivity of central vagal neurocircuits (556, 557). The reversibility of these hyperglycemia- and diabetes-induced effects on vagal neurocircuits is of particular importance for future investigations—is there a period of exposure to elevated glucose levels beyond which the damage to vagal neurocircuits is irreversible, or is the system sufficiently plastic to recover following subsequent tight glycemic control? The recent demonstration that Roux-en-Y gastric bypass surgery reverses the diet-induced obesity associated decreased in excitability and responsiveness of vagal efferent motoneurons suggests these neurocircuits are capable of a surprising degree of adaptation and that even long-term dysfunction does not necessarily result in permanent and irrecoverable rewiring of vagal neurocircuitry (71). The rapid remission of Type 2 diabetes following bariatric surgery, far in advance of weight loss, certainly implies that the recovery of glycemic regulation may be an important mechanism if the recovery of vagal afferent and efferent homeostatic control.

Spinal cord injury and Gastrointestinal Reflexes

GI dysfunction following spinal cord injury (SCI) is observed commonly in both patients and animal models at all levels of the GI tract including the esophagus (increased gastroesophageal reflux, esophagitis, and decreased esophageal contractility), stomach and upper GI tract (ulceration, dysregulated motility, altered accommodation, and delayed gastric emptying) and lower GI tract [constipation, distention; reviewed in (150,227)]. While the sympathetic innervation to the GI tract, as well as the parasympathetic innervation to the colon and rectum, is interrupted following SCI, vagal neural pathways to the stomach and upper GI are anatomically intact following spinal injury. This would suggest that the gastric and upper GI dysfunction observed following SCI occurs as the result of an indirect, rather than direct, effect upon vagal neurocircuit function.

As described above, the NTS is the recipient of both vagal and spinal sensory inputs; while the loss of spino-solitary inputs would certainly be expected to have some impact upon brainstem sensory information processing, several lines of evidence suggest that vagal afferent hypo-responsiveness following SCI may play a significant role in the observed upper GI dysfunction [reviewed in (227)] despite being anatomically intact following injury. Activation of NTS neurons in response to peripheral CCK administration is reduced following SCI and electrophysiological studies demonstrated a reduced activation of vagal sensory inputs onto NTS neurons (480). This decrease in responsiveness of vagal afferent sensory neurons may lead to chronic alterations in gut-brain signaling following SCI resulting in the observed GI and autonomic dysfunctions.

Cholinergic anti-inflammatory pathway

An increasing body of work supports the concept that the nervous and immune systems have a complex and intricate communication network, and that crosstalk between these systems is important in the regulation of immune responses [see reviews (66, 122, 123, 321, 372, 373)]. While neuroendocrine mechanisms certainly dampen and attenuate inflammatory responses via activation of the HPA axis (133, 347, 406), the idea that inflammatory responses are also

modulated via the autonomic nervous system, however, is a more recent concept. The discovery that vagal nerve stimulation suppresses cytokine production potently lead to the recognition of a vagally mediated cholinergic anti-inflammatory pathway, whereby activation of vagal afferents by inflammatory mediators results in the reflex activation of vagal efferent pathways to dampen cytokine production and assist in the restoration of immune homeostasis [reviewed in (321, 371, 373, 415, 483, 484)].

In brief, local and systemic inflammation stimulates the brainstem directly, via activation of cytokine receptors in the dorsal vagal complex and indirectly, via activation of vagal afferent fibers. Following integration of these inflammatory inputs, the assimilated signal is relayed to the adjacent DMV resulting in vagal efferent activation [reviewed in (321)]. Vagal efferent motoneurons that innervate the GI tract have recently been demonstrated to terminate within close proximity of resident macrophages (377); release of acetylcholine following vagal nerve stimulation has been shown to attenuate the inflammation and ileus resulting from intestinal manipulation [reviewed in (59)]. Intestinal mucosal integrity is also known to be critically important in homeostasis, providing a defensive barrier between food antigens and intestinal microbiota. Decreased tolerance to microbiota is a hallmark of intestinal inflammatory conditions including Crohns disease and ulcerative colitis (368) while a decreased tolerance to food antigens is associated with food intolerance and allergies (45). Under both conditions, inappropriate and exaggerated activation of the immune system leads to tissue damage and, potentially, to sepsis. Immune cells within the intestinal mucosa and submucosa, including T cells, dendritic cell, mast cells and enteric glial cells, are known to contain nicotinic acetylcholine receptors and are, therefore, potential targets of the vagal anti-inflammatory pathway (321,368). Certainly, following vagotomy, mice have an increased susceptibility to inflammatory conditions such as colitis following mucosal irritation (181–183).

While the majority of studies have examined the important role of the cholinergic anti-inflammatory pathway under pathophysiological conditions, other investigations have demonstrated that enteral lipid suppresses mesenteric cytokine release (151) possibly via actions involving activation of vagal afferent CCK receptors (130) suggesting that this vagally dependent reflex may also be activated under physiological conditions.

The spleen is known to be the major source of several cytokines involved in the pathophysiology of inflammation. Until recently, the neuroanatomy of the parasympathetic innervation to the spleen was subject to controversy; lately, however, it has been demonstrated that the vagus nerve does not innervate the spleen directly but, rather, innervates the spleen indirectly via collateral projections to the celiac ganglion (67). Acetylcholine released from these vagal efferents activates nicotinic receptors, specifically $\alpha 7$ subunit-containing nicotinic receptors, on adrenergic neurons within this prevertebral ganglion, resulting in the release of NE within the spleen; activation of splenic adrenergic receptors stimulates the production of acetylcholine from splenic T cells which, in turn, suppresses the production of immune mediators (414).

From a therapeutic standpoint, the knowledge that the CNS, via the vagus nerve, may assist in the restoration of homeostasis via the modulation of inflammatory responses provides a

means by which activation of the cholinergic anti-inflammatory pathway can be exploited to treat a variety of clinical conditions. Vagal nerve stimulation and activation of intestinal nicotinic cholinergic receptors have certainly been shown to be efficacious in the treatment of a variety of preclinical models of intestinal inflammation and sepsis [reviewed in (321)] although proof of concept in humans is still lacking.

Gut microbiome and CNS communication

The role of microbiota within the GI tract has become the focus of several recent investigations, particularly with regard to the growing awareness of the role that the microbiome plays in the development and function of the CNS and the acceptance that the microbiome plays a significant role in the modulation of the brains-gut axis [reviewed in (117,118,200)]. The pathways by which the GI microbiome modulates CNS structure and function still be remain to elucidated although, in addition to humoral and hormonal pathways, gut microbiota also appear to communicate with the CNS via neural, particularly vagal, pathways (167,191). The importance of vagal sensory (afferent) pathways in gut microbiota-brain communication have been demonstrated in several studies; for example, the ability of chronic probiotic treatment to alter GABA receptor expression in several CNS regions, including the cortex, amygdala, and LC, which modulate GI functions (see above) is dependent upon an intact vagus nerve (68) while vagotomy attenuates the anxiolytic actions of bifidobacteria in an animal model of colitis (44). Disorders of gut microbiota are associated with several CNS-dependent disorders including stress, anxiety and depression and appear to modulate cognition [see reviews by (108,118,339)]. As described above, the NTS is the recipient of vagal afferent sensory inputs; as detailed above, the extensive connections, many bidirectional, between the NTS and other hindbrain, midbrain, and forebrain structures provides a potential neuroanatomical substrate by which GI microbiota may modulate, regulate and alter “higher” CNS functions.

Conclusions

While great progress has been made regarding the role the CNS exerts upon the GI tract, there is still much to be learned regarding the interplay between different CNS areas with respect to the integration of GI homeostatic functions. Clearly, serious long-term pathophysiological consequences can result from the failure of appropriate autonomic assimilation but the precise mechanisms responsible for these outcomes remain to be discovered.

The dorsal vagal complex has a distinct and important role to play in the regulation of GI function; both vagal and some spinal sensory inputs terminate within the NTS and NTS neurons have direct and/or indirect connections with the majority of brainstem and higher CNS nuclei involved in the regulation of GI functions. The strategic location of some portions of brainstem vagal neurocircuits outside the blood-brain barrier makes them accessible to a variety of circulating hormones, neuromodulators, and cytokines which can alter the responsiveness of vagal neurons as well as alter their ability to integrate and process the vast volume of inputs they receive from the viscera as well as other CNS areas.

It is also evident that a significant degree of plasticity exists within CNS regions involved in the co-ordination and regulation of GI functions; vago-vagal reflexes in particular display a surprising degree of flexibility. While several disparate studies have suggested that altered vago-vagal reflexes may play a significant role in the development and maintenance of several pathophysiological conditions, there is much still to be learned regarding the normal physiology of vagal reflexes and the role that higher CNS centers exert upon their function. A large body of work has demonstrated that, peripherally, the activity and responsiveness of vagal sensory neurons varies according to nutritional status—the activation of vagal reflexes will depend, therefore, on ongoing metabolic and physiological conditions. Centrally, the majority of work to date investigating plasticity within central vagal neurocircuits has centered around the ability of activity within the cAMP-PKA pathway to affect modulation of inhibitory synaptic transmission—undoubtedly, it would be somewhat naïve to assume that this is the only second messenger system that can regulate the "gain" of vagal neurocircuitry and much remains to be investigated regarding the role of other neurotransmitter/neuromodulators and their second messenger systems in the manipulation and co-ordination of GI functions.

Embracing new technologies will unquestionably assist in the uncovering of the cellular mechanisms underlying the central control, regulation, and co-ordination of GI functions. The advent and continuous advancement of imaging, optogenetic, and pharmacogenetic techniques allows for the *selective* activation or inhibition of specific neuronal subpopulations or pathways; this may prove to be particularly useful and valuable when dealing with brainstem and other central neurocircuits, given their extensive, and often intermingled, afferent and efferent connections. The standardization of experimental techniques between groups of researchers would also be advantageous in comparing experimental outcomes; note, for example, the differential effects of anesthetics on gastric emptying rates (384). Species and strain differences may also be critically important in determining experimental outcomes; Sprague-Dawley, but not Fisher 344 rats, for example, show habituation to the GI effects of stress (25, 206). Results from several groups have suggested that GI responses may vary according to the time of the day and nutritional status [see reviews by (140, 451)]; consistent research outcomes may also benefit from uniform timing of experiments. Finally, the development of dependable and reliable animal models of GI diseases [e.g., FD (300)] will continue to be a priority in assisting basic and translational understanding of the central control and regulation of GI physiological, as well as pathophysiological, functions.

The vast body of currently available information serves to stress the complexity of CNS control of GI functions. To understand such a complex hierarchical control system almost certainly requires the wholehearted implementation of integrated approaches that consider the regulation of GI functions *in toto*, rather than as discrete anatomical, physiological, or neurological processes. While certainly challenging, such multi-faced, multi-disciplinary approaches may provide a means by which basic and translational approaches can combine research strategies to provide a variety of therapeutic options to treat a multitude of GI disorders.

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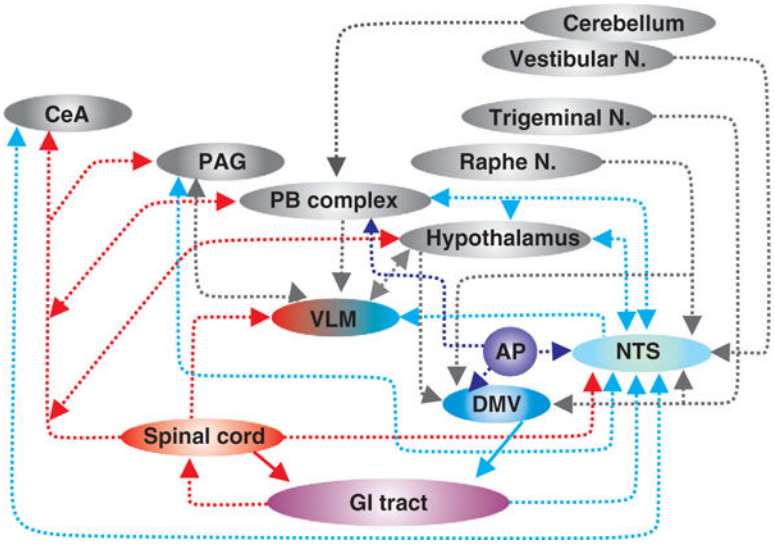

Figure 1.

Schematic representation of neuroanatomical connections between the gastrointestinal (GI) tract and central nuclei involved in the regulation of gastrointestinal functions. Note that the location of nuclei is not intended to be anatomically accurate. AP—area postrema; DMV—dorsal motor nucleus of the vagus; NTS—nucleus of the tractus solitarius; PB Complex—parabrachial complex (i.e., parabrachial nucleus + Kölliker-Fuse nucleus); PAG—periaqueductal gray; CeA—central nucleus of the amygdala; Vestibular N—vestibular nucleus; Trigeminal N—trigeminal nucleus; Raphe N—raphe nuclei.

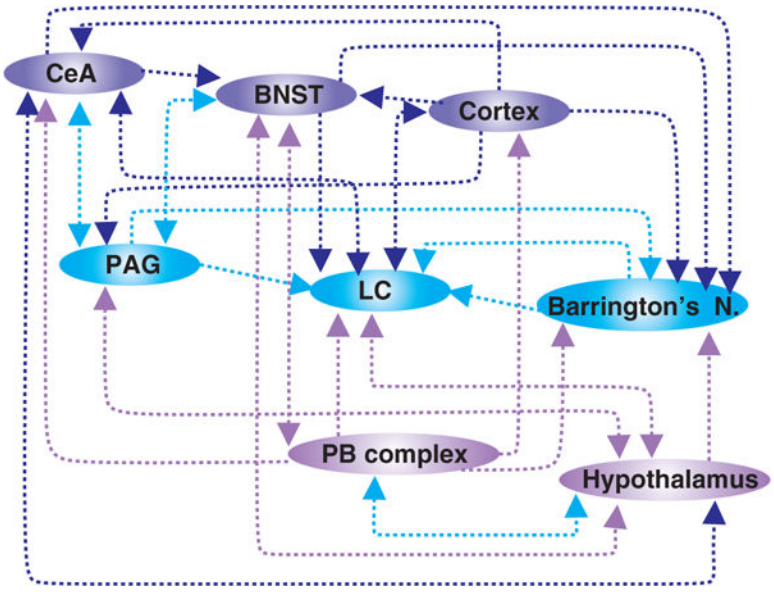

Figure 2.

Schematic representation of the neuroanatomical connections between midbrain and forebrain structures involved in the regulation of gastrointestinal (GI) functions. Note that the location of nuclei is not intended to be anatomically accurate. CeA—central nucleus of the amygdala; BNST—bed nucleus of the stria terminals; PAG—periaqueductal gray; LC—locus coeruleus; Barrington's N—Barrington's nucleus; PB complex—parabrachial complex (i.e., parabrachial nucleus + Kölliker-Fuse nucleus).

Table 1

Abbreviations

AP	Area postrema
Arc	Arcuate nucleus of the hypothalamus
BNST	Bed nucleus of the stria terminalis
CCK	cholecystokinin
CNS	Central nervous system
CRF	Corticotropin releasing factor
CSF	Cerebrospinal fluid
DMV	Dorsal motor nucleus of the vagus
DVC	Dorsal vagal complex
ENS	Enteric nervous system
FD	Functional dyspepsia
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
NANC	Nonadrenergic, noncholinergic
NPY	Neuropeptide Y
NTS	Nucleus tractus solitarius
LC	Locus coeruleus
PAG	Periaqueductal gray
PBN	Parabrachial nucleus
PVN	Paraventricular nucleus of the hypothalamus
PYY	Peptide YY
SCI	Spinal cord injury