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Musings on the Wanderer: What's New in Our Understanding of Vago-Vagal Reflex? IV. Current concepts of vagal efferent projections to the gut

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Chang, Howard Y., Hiroshi Mashimo, and Raj K. Goyal. Musings on the Wanderer: What's New in Our Understanding of Vago-Vagal Reflex? IV. Current concepts of vagal efferent projections to the gut. *Am J Physiol Gastrointest Liver Physiol* 284: G357–G366, 2003; 10.1152/ajpgi.00478.2002.—Vagal efferents, consisting of distinct lower motor and preganglionic parasympathetic fibers, constitute the motor limb of vagally mediated reflexes. Arising from the nucleus ambiguus, vagal lower motor neurons (LMN) mediate reflexes involving striated muscles of the orad gut. LMNs provide cholinergic innervation to motor end plates that are inhibited by myenteric nitrergic neurons. Preganglionic neurons from the dorsal motor nucleus implement parasympathetic motor and secretory functions. Cholinergic preganglionic neurons form parallel inhibitory and excitatory vagal pathways to smooth muscle viscera and stimulate postganglionic neurons via nicotinic and muscarinic receptors. In turn, the postganglionic inhibitory neurons release ATP, VIP, and NO, whereas the excitatory neurons release ACh and substance P. Vagal motor effects are dependent on the viscera's intrinsic motor activity and the interaction between the inhibitory and excitatory vagal influences. These interactions help to explain the physiology of esophageal peristalsis, gastric motility, lower esophageal sphincter, and pyloric sphincter. Vagal secretory pathways are predominantly excitatory and involve ACh and VIP as the postganglionic excitatory neurotransmitters. Vagal effects on secretory functions are exerted either directly or via release of local mediators or circulating hormones.

enteric nervous system; gastrointestinal motility; gastrointestinal secretions; gastrointestinal smooth muscle; neurotransmitters; parasympathetic nerves

THE VAGUS NERVE IS A MIXED sensory and motor cranial nerve; it is comprised of an extensive network of afferents fibers that transmit sensory information to the brainstem and efferent fibers that form the motor limb of vago-vagal reflexes on target organs. In recent years, there have been several important advances in our understanding of the distribution and the effects of vagal efferents on the gut. The purpose of this review is to summarize our current understanding of the role of vagal efferents in regulating motor and secretory functions of the gut that are mediated by vago-vagal and other vagal reflexes.

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CENTRAL ORGANIZATION OF VAGAL MOTOR NEURONS

Extensive work using labeling tracers such as horseradish peroxidase and fluorescent carbocyanine dye have demonstrated that vagal efferent fibers innervating the gut originate from two brain stem nuclei: the nucleus ambiguus (NA) (3) and the dorsal motor nucleus of the vagus (DMN) (1). Although some first-order afferents may make monosynaptic contacts directly with the dendrites of DMN neurons, most of the first-order vagal afferents initially project onto interneurons in selective subnuclei of the nucleus of the solitary tract (NTS). Vagal motor neurons in the NA and the DMN receive afferent inputs predominantly from NTS neurons, either as fiber projections from the NTS neurons or by sending their own dendrites into the NTS (3).

Within the DMN, the preganglionic neurons are organized into a series of columns or subnuclei that relay central outflow to gastrointestinal organs in a topographical manner (1). These columns of cells align longitudinally over the entire nucleus. Each column of cells corresponds to different organs within the gut and transmits signals to those organs via the various branches of the vagus nerve. Retrograde tracers injected into the five abdominal branches of the vagus nerve can be localized topographically in distinct columns of cells within the DMN (Table 1) (1). Although each branch of the abdominal vagal nerve supplies different organs in the abdomen, there is significant

overlap in the territories covered. In addition to this general organization, the preganglionic neurons are arranged so that neurons triggering excitatory and inhibitory vagal responses are located in different parts of the DMN. Neuroanatomical details of how preganglionic neurons forming the excitatory and inhibitory vagal pathways to different segments of the gut are arranged have become available recently.

VAGAL LOWER MOTOR NEURONS

The rostral part of the NA, called the nucleus retrofacialis or the compact formation, contains all the vagal lower motor neurons (LMN) that control the motor function of striated muscles of the pharynx and the esophagus. These LMNs mediate all of the pharyngeal and laryngeal vagal reflexes (see Table 1). In some animal species such as the mouse, rat, and dog, nearly the entire esophagus is composed of striated muscle except the most distal part. In contrast, the cat, ferret, and opossum have striated muscle only in the more proximal esophagus. In humans, only the cervical esophagus is made up of the striated muscle; the thoracic esophagus is composed of smooth muscle fiber. Regardless of the extent, all striated muscle of the esophagus receives input from LMNs located in the NA (3).

All vagal LMNs are cholinergic and excitatory in nature. The LMNs to pharynx and esophagus contain acetylcholine transferase and CGRP. Their axons are myelinated, and they make direct contact with striated muscle fibers in the cervical esophagus via motor end plates. ACh released at the motor end plate activates nicotinic cholinergic receptors on the striated muscle to initiate muscle contraction. Basal closure of the upper esophageal sphincter (UES) is generated by tonic excitation of the vagal LMNs to the cricopharyngeus and inferior pharyngeal constrictor muscles. UES opening with swallowing is due to central inhibition of these neurons and stimulation of the vagal and nonvagal neurons to the suprahyoid muscles.

Peristalsis in the striated muscle portion of the esophagus is centrally generated and mediated by vagal LMNs. Peristalsis in this region is abolished by vagotomy above the pharyngoesophageal branches. Because electrical stimulation of the vagal LMN efferents can only generate simultaneous contractions at all levels of the striated muscle (10), central organization is necessary to produce peristaltic contractions. Highly organized discharges from premotor swallowing neurons in the central subnucleus of the NTS initiate a sequential activation of vagal LMNs. This serial activation of the neurons innervating progressively distal regions results in ordered waves of striated muscle contractions in a craniocaudal direction that constitute the peristaltic contraction (Fig. 1).

In the striated muscle portion of the esophagus, the cholinergic vagal LMNs are negatively regulated by the myenteric nitrergic neurons. The striated muscle portion of the esophagus includes myenteric plexus with neurons that contain nitric oxide (NO) synthase (NOS). These neurons do not appear to be innervated by vagal preganglionic efferents but may receive local sensory inputs. The nitrergic myenteric neurons may provide peripheral inhibitory modulation of peristaltic contractions by sending inhibitory projections to the motor end plates of the striated muscles.

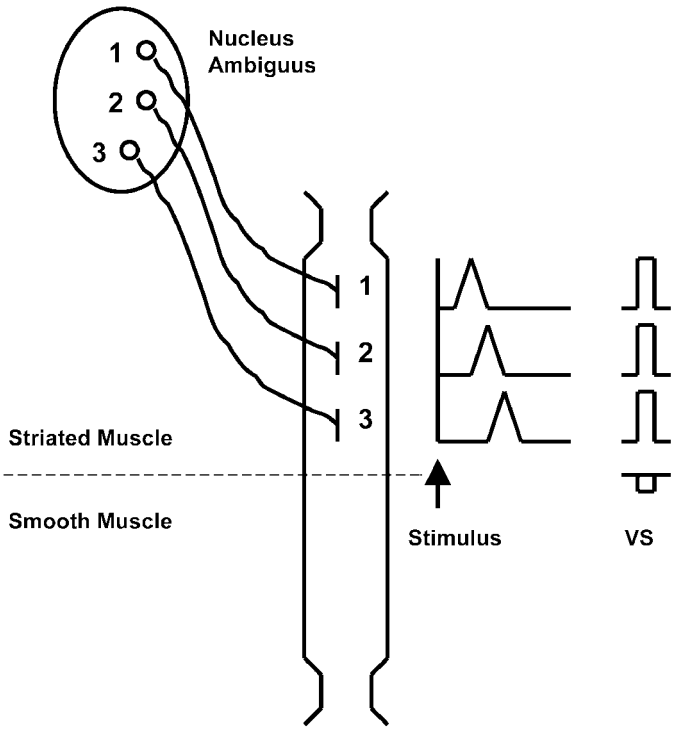

Fig. 1. Mechanism of vagally evoked peristalsis in the striated muscle of the esophagus. Peristalsis in the striated muscle portion of the esophagus is centrally generated by the nucleus ambiguus and mediated by vagal lower motor neurons. The nucleus ambiguus generates a sequential activation of vagal lower motor neurons, which, in turn produce successive contractions in the cervical esophagus in a proximodistal direction. vs, Vagal stimulation.

VAGAL PARASYMPATHETIC PREGANGLIONIC NEURONS

The DMN contains all the preganglionic neurons that project onto postganglionic neurons, which, in turn, innervate the smooth muscle, exocrine glands, and endocrine cells of the upper and midgut (Table 1). The postganglionic neurons supplying the distal colon, rectum, and the anal canal receive input from the sacral cord. Preganglionic neurons in the DMN form the motor limb of vagal-mediated reflexes involving smooth muscle organs of the gut. Their axons are usually unmyelinated and transmit impulses at C-fiber conduction velocities. The axons terminate on the enteric plexus neurons. It is important to emphasize that the enteric secretomotor neurons that are postganglionic neurons in the vagal pathway also receive concomitant inputs from enteric neurons, sympathetic nerves, systemic hormones, and local mediators.

The number of postganglionic neurons involved in the vagal pathways is only a small portion of the total number of enteric neurons in the gut. It was initially proposed that all of the neurons in the myenteric and submucosal ganglia of the gut were postganglionic neu-

Table 1. *Vagal efferent connections*

Nucleus of Origin	Type of Neuron	Branches of Vagus Nerve	Organs Innervated
NA	LMN	Pharyngeal branches	Muscles of palate and lower pharynx (palatoglossus, levator veli palatini, uvular muscles). Muscles from pharyngeal constrictor and palatal regions.
NA	LMN	Superior laryngeal nerve branches	
		Internal branch	Striated muscle fibers of larynx
NA	LMN	External branch	Cricothyroid muscle
NA	LMN	Recurrent laryngeal nerve branches	
		Somatic component	Intrinsic muscles of larynx (lateral and posterior cricoarytenoids, thyroarytenoid, and interarytenoid muscles) except cricothyroid. Striated muscle portion of the esophagus.
NA	Preganglionic	Parasympathetic component	Larynx below vocal folds, trachea, and upper esophagus
NA, IZ, DMN	Preganglionic	Cervical pulmonary branches	Smooth muscle of lungs. Pulmonary artery and vein
NA, IZ, DMN	Preganglionic	Cervical cardiac branches	Atria, aorta, vena cava
NA, IZ, DMN	Preganglionic	Superior laryngeal nerve branches	
		External branch	Larynx above vocal folds
DMN	Preganglionic	Internal branch	Mucous glands of larynx
DMN	Preganglionic	Gastric branches	Stomach and proximal duodenum
DMN	Preganglionic	Hepatic branch	Minor parts of distal antrum, duodenum, liver and gallbladder
DMN	Preganglionic	Celiac branches	Duodenum, jejunum, ileum, cecum, and colon

NA, nucleus ambiguous; IZ, intermediate zone; DMN, dorsal motor nucleus of vagus nerve; LMN, lower motor neuron.

rons in the vagal efferent pathways. However, because the number of enteric neurons is significantly greater than the number of vagal efferent fibers, it became clear that the preganglionic efferents cannot possibly provide direct input to all of the enteric neurons. Moreover, functional and morphological studies suggest that there are regional differences in the density of vagal preganglionic innervation along the gut. Vagal influence is more prominent in the esophagus and stomach but decreases in the small bowel and colon. Anterograde tracers injected into the DMN have been shown to label up to 100% of the myenteric ganglia in the stomach, 96% in the duodenum, 40% in the jejunum, 66% in cecum, 16% in the descending colon, and 0% in the rectum (Fig. 2) (2).

Vagal efferents to gastrointestinal smooth muscles provide parallel inhibitory and excitatory stimuli. For a long time in the past, it was thought that the vagus nerve provides only excitatory influences to the gut. One of the major advances in our understanding of how the vagus nerve controls gastrointestinal motility is the realization that vagal motor pathways are comprised of parallel inhibitory and excitatory pathways (4, 16). The neurons that constitute the inhibitory and excitatory pathway to each organ appear to be segregated within the DMV (Fig. 3). These pathways have been best characterized for the lower esophageal sphincter (LES). The preganglionic neurons of the excitatory motor pathway are localized to the rostral DMN, whereas preganglionic neurons of the inhibitory motor pathway are present in the caudal part of the DMN (17). Information on the location of neurons forming the inhibitory and excitatory vagal pathways to other parts of the gut is currently incomplete. The smooth muscle of the gut also receives segmental innervation that allows discrete vagal control over different motor segments within the same organ, similar to that for the striated muscles. Anatomic details of such segmental pathways are also not currently known.

The excitatory vagal pathway consists of preganglionic cholinergic neurons and postganglionic cholinergic neurons containing cholineacetyltransferase and substance P. In contrast, the inhibitory motor pathway consists of preganglionic cholinergic neurons and postganglionic nonadrenergic, noncholinergic (NANC) neurons that contain NOS and VIP. These neurons exert inhibitory effects

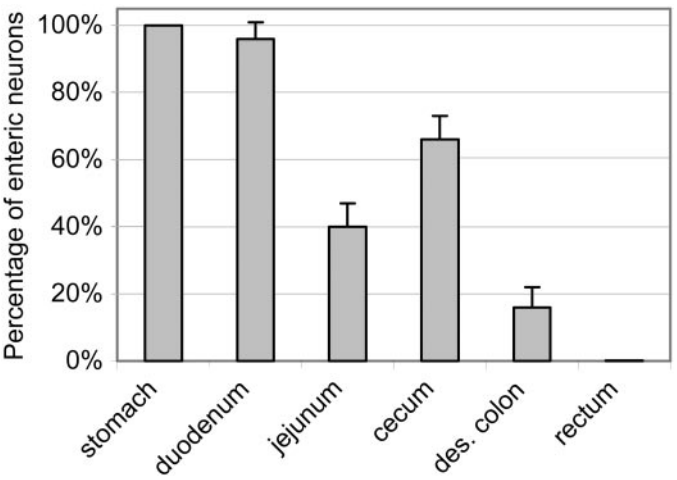

Fig. 2. Decreasing density of the enteric neurons that are innervated by the vagal preganglionic fibers. The figure shows the percentage of vagally innervated myenteric ganglia in different sections of the gastrointestinal tract. Vagal efferents demonstrate a gradient of generally decreasing innervation at distal segments of the gut. Vagal influence is maximal at the stomach and proximal duodenum and decreases in the mid- and the distal gut. des, Descending.

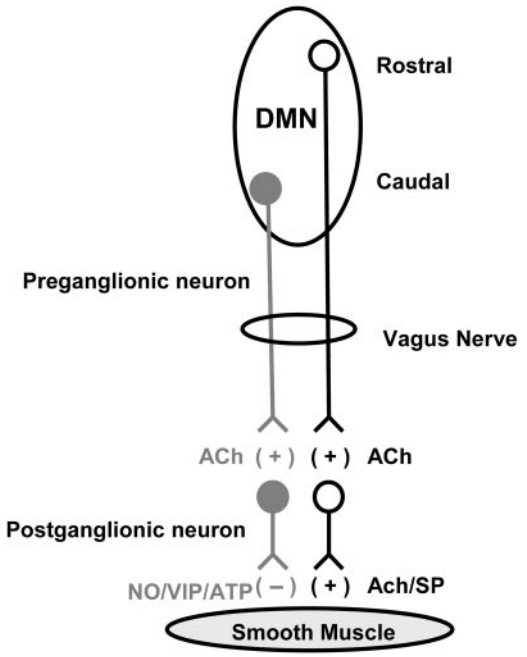

Fig. 3. Parallel excitatory and inhibitory pathways. Vagal preganglionic efferents to the gut form 2 pathways: *1*) excitatory pathway with cholinergic preganglionic neurons from the rostral dorsal motor nucleus (DMN) and cholinergic postganglionic neurons in the enteric ganglia; *2*) inhibitory pathway with cholinergic preganglionic neurons from the caudal DMN and nitrergic postganglionic neurons in the enteric ganglia. Smooth muscle tone is dependent on the balance between the 2 pathways. NO, nitric oxide; SP, substance P.

on smooth muscle by releasing ATP, NO, and VIP. The synaptic transmission between the preganglionic cholinergic neurons and the postganglionic neurons involves nicotinic as well as muscarinic receptors.

The vagal influence on the motor activity of gastrointestinal viscera is dependent on the organ's background motor activity and whether the inhibitory, excitatory, or combination of both inhibitory and excitatory vagal pathways is involved. The inhibitory and excitatory vagal motor pathways act independently in some reflex activities, whereas in others, they act in concert to produce a complex motor response. For example, the smooth muscle sphincters of the gut remain contracted in the basal state due to their intrinsic myogenic tone. Activation of the inhibitory vagal pathways to the sphincters causes relaxation, whereas stimulation of the excitatory pathways causes contraction. A sequential activation of inhibitory and excitatory vagal pathways produces a sequence of relaxation followed by contraction. The vagal pathways also innervate and regulate the activity of the intramural interstitial cells of Cajal, which are endocrine cells that exert effects on gastrointestinal smooth muscle either by a direct action or by releasing local mediator or circulating hormone.

PERISTALSIS IN ESOPHAGEAL SMOOTH MUSCLE

In the smooth muscle portion of the esophagus, swallowing elicits reflex peristalsis that is generated centrally and mediated by preganglionic vagal neurons from the DMN. Swallow-induced peristalsis is termed primary peristalsis to distinguish it from the so-called secondary peristalsis that is produced by local reflexes. Primary peristalsis is abolished by bilateral vagotomy. Vagal preganglionic efferents stimulate peristalsis by activating and modifying the intrinsic esophageal peristaltic reflex.

The intrinsic esophageal peristalsis is mediated by the NANC inhibitory and cholinergic excitatory myenteric neurons acting in concert. Although usually termed inhibitory, stimulation of the NANC nerves in smooth muscle strips elicits a biphasic response that consists of inhibition followed by a rebound contraction. In smooth muscles that have no basal tone, inhibition is expressed only as a latency period during the period of nerve stimulation. Contraction of smooth muscle follows the end of a prolonged stimulus and is called the "rebound" or "off" contraction. Weisbrodt and Christensen (24) showed that the latencies of the rebound contraction in esophageal circular muscle strips increase progressively in a craniocaudal orientation and proposed that a latency gradient along the esophagus is generated by NANC nerves. Recent studies demonstrate that NO is the elusive NANC neurotransmitter responsible for the biphasic response. NOS inhibitors suppress the latency and latency gradient of esophageal contractions due to NANC nerve stimulation at different levels of the esophagus (14).

Excitatory postganglionic neurons that are cholinergic in nature are also present in the esophageal myenteric plexus (9). The cholinergic neurons demonstrate a gradient of influence that decreases distally along the esophagus (4). In most experimental protocols, cholinergic and NANC nerves are stimulated simultaneously. With simultaneous activation by a short-duration nerve stimulus, the NANC inhibitory response appears first and is followed by a cholinergic contraction that may overlap the NANC rebound contraction. When the nerve stimulus is prolonged, the cholinergic contraction and the NANC rebound contractions become separated. The cholinergic contraction occurs near the onset of the stimulus and is called the "on" contraction; the NANC rebound contraction occurs at the end of the stimulus and is called the off contraction.

Crist et al. (4) presented a model that incorporates the gradients of increasing NANC and decreasing cholinergic influences along the esophagus. This model explains the peripheral mechanisms for peristalsis-like behavior of esophageal circular muscle strips in vitro, and esophageal peristalsis elicited by vagal efferent stimulation in vivo (Fig. 4).

The swallowing reflex that evokes primary peristalsis is organized by the swallowing center in the brain stem and is conveyed to the esophageal smooth muscles by vagal preganglionic neurons. With the onset of swallowing, preganglionic efferents that project onto the NANC postganglionic neurons are activated first. These efferents cause a prompt inhibition of the entire smooth muscle esophagus that occurs within <1 s of the onset of swallowing. This phenomenon is termed deglutitive inhibition. The degree and duration of the

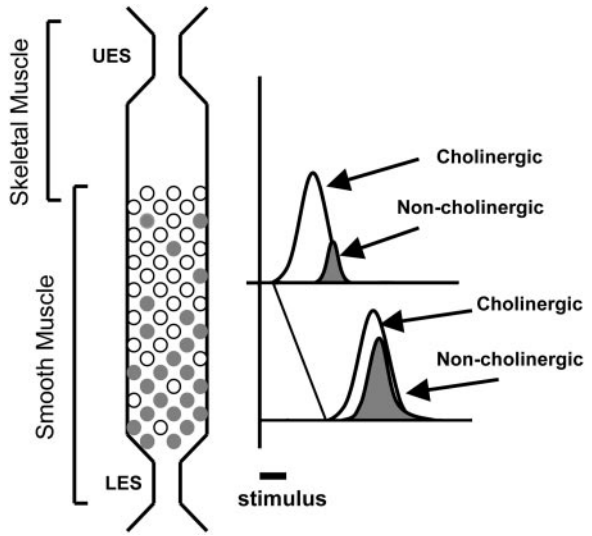

Fig. 4. Peripheral mechanism of peristalsis. Crist's model (4) describes gradients of cholinergic and noncholinergic nerve influence along the smooth muscle portion of the esophagus. Cholinergic influence predominates at the proximal esophagus and decreases distally. In contrast, noncholinergic influence is minimal proximally and progressively increases at the distal esophagus. UES, upper esophageal sphincter; LES, lower esophageal sphincter.

inhibition are greater at the distal end of the esophagus due to the gradient of increasing NANC influence. The inhibitory response is followed by a rebound contraction with progressively increasing latencies along the esophagus. Swallowing also initiates the sequential activation of a second set of preganglionic efferent fibers with latency periods ranging between 1 and 5 s (7). These fibers with longer latencies are speculated to project onto cholinergic postganglionic excitatory neurons in the esophagus. This sequential activation of the cholinergic excitatory pathway is similar to the serial activation of the lower motor neurons in the striated muscle of the esophagus. During swallowing, the cholinergic excitation sequence is timed to superimpose on the NANC rebound contraction. This augments the amplitude and modulates the latency gradient of the primary peristaltic contraction (Fig. 5).

In humans, deglutitive inhibition preceding the primary peristalsis is prominently revealed when repetitive successive swallows are taken at close intervals, as seen when drinking fluids. Each successive swallow inhibits the peristaltic contraction from the preceding swallow, and only the last swallow is associated with peristaltic contraction.

LES

The LES is composed of tonic smooth muscle with intrinsic myogenic properties that keep the sphincter closed during basal conditions. Manometrically, the LES is revealed as a zone of high pressure that is present at the lower end of the esophagus. Vagal preganglionic fibers projecting to the LES arise from two distinct populations of cells in the DMN, one rostral and one caudal to the obex. The preganglionic neurons that form the inhibitory pathway are located in the caudal regions of the DMN, whereas the neurons for the excitatory pathway are concentrated in the rostral part of the DMN (17). The synaptic neurotransmission between the preganglionic cholinergic and the postganglionic nitrergic neurons involves nicotinic and m_1 muscarinic receptors. Furthermore, the neurotransmission of the excitatory postganglionic neurons is cholinergic and peptidergic (substance P), whereas the inhibitory postganglionic neurons are nitrergic and peptidergic (VIP).

Both the inhibitory and the excitatory vagal pathways exert tonic effects on the LES (Fig. 6). When the inhibitory and excitatory influences are equal, bilateral vagotomy (9) or the use of tetrodotoxin (8) does not change the lower esophageal pressure. On the other hand, selective antagonism of only one of the pathways leads to unopposed effects of the other pathway. For example, suppression of a cholinergic excitatory pathway by an anticholinergic agent or botulinum toxin decreases LES pressure due to the unopposed action of the inhibitory nerves. In contrast, suppression of a nitrergic inhibitory pathway with NOS inhibitors results in a rise in the LES pressure due to the unopposed action of the excitatory nerves.

Selective activation of the vagal inhibitory pathway can generate the reflex LES relaxation associated with deglutition. LES relaxation is an integral part of swallow-evoked primary peristalsis, and both the LES relaxation and primary peristalsis are abolished by bilateral vagotomy. With the onset of swallowing, LES relaxes to intragastric pressure. This relaxation lasts

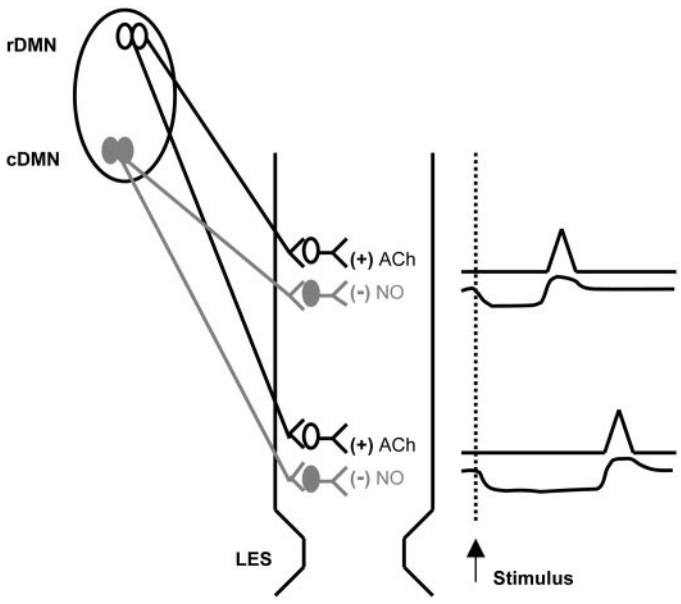

Fig. 5. Role of vagal efferent nerves in primary peristalsis. Sequential activation of nonadrenergic, noncholinergic (NANC) and cholinergic postganglionic neurons in the smooth muscle portion of the esophagus accounts for deglutitive inhibition followed by peristalsis. Short-latency fibers activate NANC postganglionic neurons to produce smooth muscle inhibition initially. Long-latency fibers subsequently stimulate cholinergic neurons to produce muscle contractions that are timed to coincide with NANC rebound contractions. rDMN, rostral DMN; cDMN, caudal DMN.

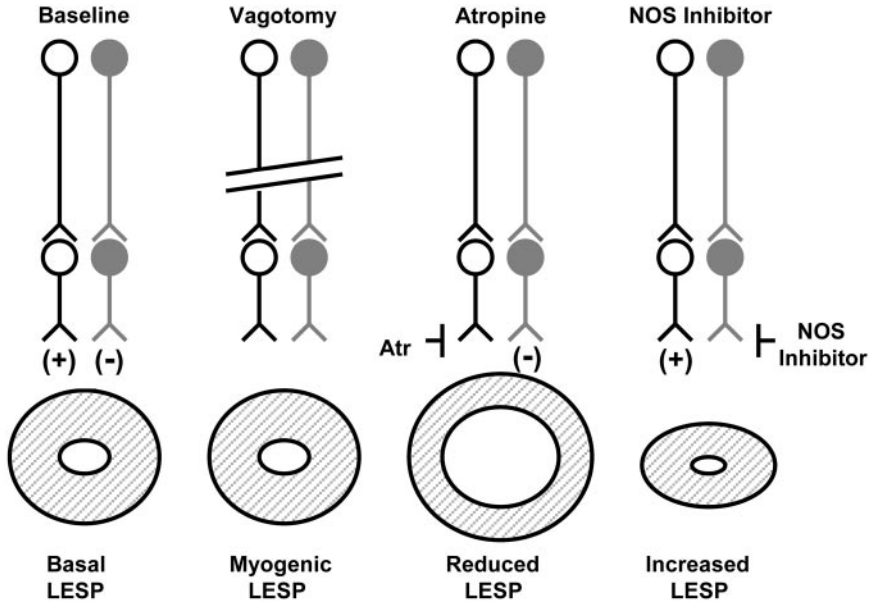

Fig. 6. Effect of vagotomy and neural antagonists on the lower esophageal sphincter pressure (LESP). LESP is dependent on the balance between vagal excitatory and inhibitory pathways. Changes in the LESP can be caused by defects in inhibitory, excitatory, or both inhibitory and excitatory vagal pathways. Bilateral vagotomy and tetrodotoxin reveal myogenic LESP, because both excitatory and inhibitory pathways are disrupted equally. Botulinum toxin selectively inhibits the excitatory pathway and reduces LESP. Conversely, NO synthase (NOS) inhibitors selectively interrupt the inhibitory pathway and increase LESP. Atr, atropine.

for ~8–10 s and is followed by an aftercontraction in the rostral part of the LES that is continuous to the peristaltic contraction in the esophageal body. This series of events enables the swallowed bolus to pass through the high-pressure LES with minimal resistance and restores the barrier to gastric contents immediately afterwards. LES relaxation is the most sensitive component of the primary peristaltic reflex, because the relaxation can occur without associated pharyngeal or esophageal peristalsis. Minimal pharyngeal stimulation can cause LES relaxation that may be clinically important in the pathogenesis of gastroesophageal reflux in the pharyngeally intubated patients.

Vagal inhibitory and excitatory pathways to the LES are selectively activated in a number of motor reflexes involving the LES. Stimulation of abdominal vagal afferents and distension of the proximal stomach trigger the inhibitory pathway to produce LES relaxation. Vago-vagal reflexes such as belching and the so-called transient LES relaxation also rely on the inhibitory pathway to generate LES relaxation (Fig. 7). Conversely, activation of the vagal excitatory pathway increases the LES pressure and myoelectric phasic contractions, which have been recorded in the LES during phases II and III of gastric migrating motor complexes.

Of note, vagotomy does not affect the LES relaxation produced by distension of the smooth muscle portion of the esophagus, with or without the associated secondary peristalsis that stems from the local reflex pathway (9). This contrasts sharply with the abolishing effect of vagotomy on LES relaxation elicited by distension of the striated muscle part of the esophagus (12). This is due to the fact that secondary peristalsis in striated muscle is centrally mediated via the brain stem.

PROXIMAL STOMACH

Vagal efferents play an important role in modulating the tonic contractions of smooth muscles in the proximal stomach. The vagal inhibitory pathway is essential to the receptive relaxation reflex that is designed to accommodate ingested food with minimal increases in the gastric pressure. Bilateral cervical vagotomy completely abolishes the receptive relaxation in cats and dogs. Electrical vagal stimulation induces gastric fundic relaxation (21). However, selective stimulation of vagal preganglionic fibers projecting onto postganglionic cholinergic neurons can increase proximal stomach tone and enhance gastric emptying of liquids.

Interestingly, esophageal distension may also cause gastric fundic relaxation. It has been suggested that esophageal distension, via vagal afferents and the central subnucleus of the NTS, stimulates the vagal inhibitory pathway neurons in the caudal DMN and inhibits the excitatory pathway neurons in the rostral part of the DMN (16). The summation of these two effects leads to proximal stomach relaxation in response to esophageal distension.

The so-called adaptive relaxation reflex refers to the relaxation of the proximal stomach in response to gastric antral distension. Adaptive relaxation is responsible for creating a pressure gradient within the stomach that promotes retropulsion of food to ensure that large food particles are adequately triturated. The adaptive relaxation can be generated by a local reflex as well as by vago-vagal pathways. Afferent signals from mechanoreceptors in the antrum are relayed to the NTS and DMN sequentially. Vagal preganglionic neurons innervate the NANC inhibitory neurons in the myenteric plexus of the proximal stomach. Bilateral vagotomy results in transient loss of adaptive relaxation that is restored with time in rats (22).

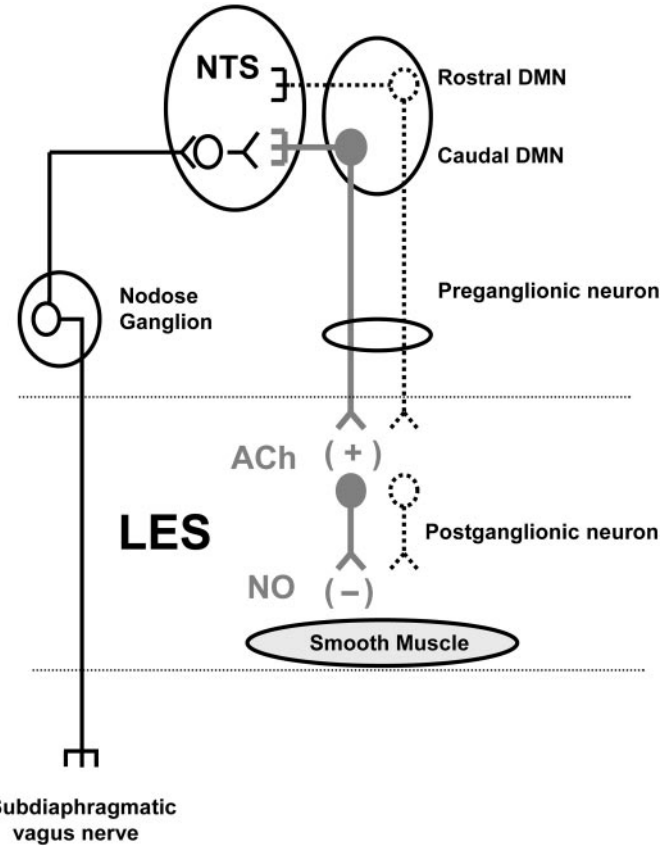

Fig. 7. Neural circuitry for transient LESR (tLESR). Afferent signals from the subdiaphragmatic vagus nerves are relayed sequentially to the nucleus of the solitary tract (NTS) and the DMN. LES relaxation results from the selective activation of the vagal inhibitory pathway, which increases NO release from postganglionic neurons.

DISTAL STOMACH

The distal stomach, including the distal two-thirds of the corpus and the antrum, exhibits phasic contractions paced by slow waves and migrating motor complexes (MMC). The main purpose of phasic contractions in the distal stomach is to grind food into smaller particles that can be emptied into the duodenum. Vagal excitatory pathway augments these phasic contractions. In the rat, vagotomy delays the antral contractions in response to feeding and reduces them 40 min after feeding (11). Although gastric MMC is not initiated by the vagus nerve, vagal efferents modulate its character (23). Gastric MMC has been shown to be inhibited by vagal denervation and stimulated by vagal stimulation. Vagal denervation decreases the number of contractions and total motor activity of the MMC (23). The vagal excitatory pathway acts to promote MMC in the stomach.

PYLORUS

Both of the vagal excitatory and inhibitory pathways assist in regulating the pyloric sphincter. The vagal excitatory pathway contributes toward the closure of pylorus sphincter during the initial prandial phase when the antrum displays phasic contractions. Subsequently, in the late prandial phase, the vagal inhibitory pathway generates pyloric relaxation and lowers the pyloric resistance to promote flow of triturated food into the duodenum. During gastric emptying, vagal efferent nerves coordinate the motor sequence of antral contraction followed by pyloric opening. Vagotomy impairs antropyloric coordination and delays gastric emptying (11).

GALLBLADDER AND SPHINCTER OF ODDI

Vagal efferent nerves form a rich network of nerve fibers around the gallbladder and sphincter of Oddi. Recent morphological studies have shown that the gallbladder is innervated by inhibitory vagal preganglionic neurons situated at the caudal DMN and by excitatory vagal preganglionic neurons localized to the rostral DMN (5). This arrangement of inhibitory and excitatory vagal pathways to the gallbladder is similar to that seen for the LES.

The effect of the vagus nerve on the motility of the gallbladder is controversial. Numerous studies have shown that truncal vagotomy results in impaired gallbladder emptying, whereas others reported no effects. These conflicting results may be due to the variation in the amount of vagal excitatory and inhibitory pathways that are affected during those studies. In the presence of a prominent excitatory vagal component, vagotomy inhibits the increase in spike potentials in the sphincter of Oddi (20) and disrupts the interdigestive motor activity of the gallbladder that is usually coordinated with gastric MMC (25). Both of these mechanisms contribute toward impaired gallbladder emptying. In contrast, it is possible that in the presence of a prominent inhibitory vagal component, vagotomy merely reflects the lack of excitatory vagal influence and results in no effect on gallbladder motility. Further studies are needed to test this possibility.

SMALL INTESTINE

The small intestine exhibits rhythmic phasic contractions, MMC, and giant migrating contractions (GMC). The rhythmic phasic contractions of the small intestine produce slow, orderly propulsion of luminal contents in an aboral direction. Stimulation of vagal stimulation in the neck causes a sequence of inhibition followed by excitation of the phasic activity (Fig. 8) (6).

The role of vagal efferents in regulating the MMC of the small intestine is not fully understood. It has been suggested that vagal inhibitory activity is more active in the proximal small intestine, which acts to slow the progression of MMC through the bowel. Vagal efferent stimulation with sham feeding suppresses MMC and inhibits propagation of MMC (15). This contrasts sharply with the excitatory effect of vagal stimulation on gastric MMC.

GMC are motor patterns exhibiting large amplitudes and long durations that normally occur only in the distal small bowel and colon. However, under certain circumstances such as bowel infection, GMC may

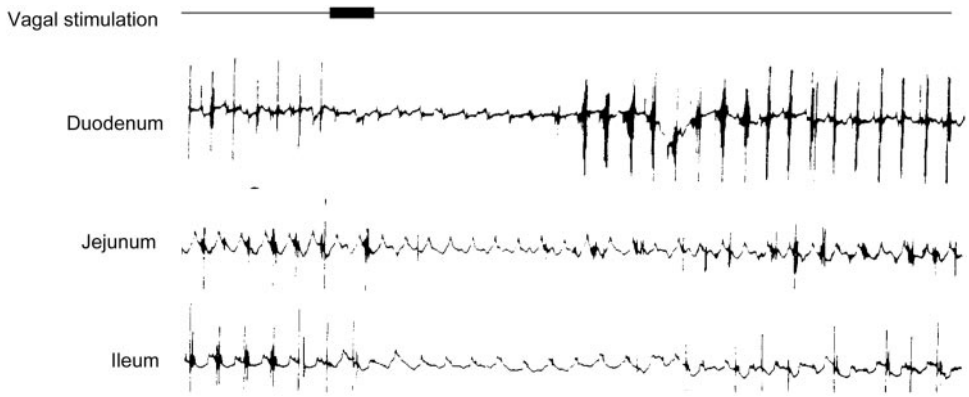

Fig. 8. Effect of vagal stimulation on small intestine electrical activity. Vagal stimulation produces a sequence of electrical inhibition followed by excitation that stems from stimulating vagal inhibitory and excitatory pathways, respectively (Adapted from Ref. 6).

sweep through the entire gut. Sha et al. (19) reported that origination and retrograde migration of GMC associated with vomiting induced by apomorphine in the small intestine are suppressed by vagotomy.

ILEOCECAL SPHINCTER

The ileocecal sphincter (ICS), a high-pressure zone that serves as a barrier preventing reflux of colonic content into the ileum, has been shown to demonstrate

Table 2. *Effect of vagal stimulation and vagotomy on endocrine and exocrine glands of the gastrointestinal tract*

Organs (Secretory Substance)	Target Cells	Effect of Vagal Stimulation on Endocrine Cells	Effect of Vagal Stimulation on Exocrine Cells	Effect of Vagotomy
Salivary glands				
Salivary amylase	Acinar cells		Increase salivary amylase secretion	Decrease amylase secretion
Salivary bicarbonate	Ductal cells		Increase salivary bicarbonate secretion	Decrease salivary amylase secretion
Stomach				
Gastric bicarbonate	Mucosal cells		Increase bicarbonate secretion	
HCI	Parietal cells		Increase acid secretion	Decrease acid secretion
Pepsinogen	Chief cells		Increase pepsinogen secretion	Abolish pepsinogen secretion
Histamine	ECL cells	Increase histamine secretion	Increase acid secretion	Inconclusive
Gastrin	G cells	Increase gastrin secretion	Increase acid secretion	Increase serum gastrin level
Somatostatin	D cells	Inhibit somatostatin secretion	Increase acid secretion	Inconclusive
Pancreas				
Amylase	Acinar cells		Increase amylase secretion	Inconclusive
Chymotrypsin	Acinar cells		Increase chymotrypsin secretion	
Lipase	Acinar cells		Increase lipase secretion	Inconclusive
Trypsin	Acinar cells		Increase trypsin secretion	Inconclusive
Pancreatic bicarbonate	Ductal cells		Increase bicarbonate secretion	Decrease bicarbonate secretion
Glucagon	A cells	Increase glucagon secretion	Induce glucogenogenesis and glycolysis	Decrease glucagon secretion
Insulin	B cells	Increase insulin secretion	Increase uptake of glucose	Inconclusive
Somatostatin	D cells	Inhibit somatostatin secretion	Stimulate pancreatic secretion	Inconclusive
Pancreatic polypeptide	F cells Acinar cells	Increase pancreatic polypeptide secretion	Inhibit pancreatic secretion	Decrease pancreatic polypeptide secretion
Small intestine				
Duodenal bicarbonate	Mucosal cells		Increases duodenal bicarbonate secretion	
Serotonin	Enterochromaffin cells	Increase serotonin secretion	Increase pancreatic secretion	
Colon				
Peptide YY	Acinar cells	Increase peptide YY secretion	Inhibit gastric acid and pancreatic secretion	Inconclusive

ECL, enterochromaffin-like.

both tonic and phasic contractions. Vagal efferents regulate the motor activities of the ICS in conjunction with splanchnic and intramural nerves. Electrical stimulation of vagal efferent nerves induces a biphasic response in which the ICS exhibits a rebound contraction after an initial relaxation. By altering the frequency of vagal stimulation, both sphincter relaxation and contraction can be elicited independently. When chyme is propagated through the small intestine to the ICS, the vagal inhibitory pathway relaxes the sphincter to permit flow through into the sphincter. The vagal excitatory pathway subsequently activates tonic contraction to close the sphincter (13). Elevations in tonic pressure across the ICS are associated with phasic contractions.

PROXIMAL COLON

Phasic contractions, MMCs, and GMCs have been described in the proximal colon. Cervical vagal cooling greatly reduces colonic motility, and vagal stimulation elicits large-amplitude colonic contractions (18).

DISTAL COLON

The distal colon does not receive vagal preganglionic innervation. Instead, it is innervated and regulated by spinal preganglionic neurons located in the sacral segments of the spinal cord.

VAGAL REGULATION OF UPPER GASTROINTESTINAL SECRETIONS

In contrast to the parallel-pathway model seen in the motor regulation of smooth muscle viscera, vagal efferent pathways to secretory cells throughout the gut exhibit mostly excitatory effects. Unlike vagal innervation of the smooth muscles, direct inhibitory innervation is not present. Both postganglionic cholinergic and VIPergic neurons in the enteric ganglia provide excitatory stimuli for secretory cells. Some postganglionic neurons provide direct stimulation to the exocrine secretory cells, whereas other secretory effects are mediated by the release of intermediary factors or circulating hormones. Table 2 summarizes the effects of vagal stimulation and vagotomy on the secretory activity in the gastrointestinal tract.

SUMMARY

In conclusion, our understanding of how vagal efferent nerves regulate motor and secretory functions of the gut has increased significantly in recent times. The most important discovery regarding vagal regulation of smooth muscles in the gut is the realization that vagal preganglionic neurons form two separate excitatory and inhibitory pathways by innervating different postganglionic neurons in the enteric ganglia. This parallel innervation enables vagal efferent nerves to induce changes in smooth muscle tone by selectively activating excitatory, inhibitory, or both pathways. Both excitatory and inhibitory pathways are necessary because different smooth muscle organs in the gut have varying baseline muscle tone and different motor complexes. In contrast, vagal pathways to secretory cells in the gut predominantly produce excitatory responses. Only excitation of secretory cells is needed, because they are quiescent during basal conditions. More investigation is needed to delineate the locations of inhibitory and excitatory neurons in the DMN, the mechanisms by which the pathways are selectively activated, the anatomical connections to the enteric nervous system, and the types of neurotransmitters released by postganglionic neurons. Furthermore, more studies are needed to understand the role of vagal efferent nerves in the regulation of gastrointestinal motility.

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