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Physiology of Normal Esophageal Motility

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Abstract

The esophagus consists of two different parts. In humans, the cervical esophagus is composed of striated muscles and the thoracic esophagus is composed of phasic smooth muscles. The striated muscle esophagus is innervated by the lower motor neurons and peristalsis in this segment is due to sequential activation of the motor neurons in the nucleus ambiguus. Both primary and secondary peristaltic contractions are centrally mediated. The smooth muscle of esophagus is phasic in nature and is innervated by intramural inhibitory (nitric oxide releasing) and excitatory (acetylcholine releasing) neurons that receive inputs from separate sets of preganglionic neurons located in the dorsal motor nucleus of vagus. The primary peristalsis in this segment involves both central and peripheral mechanisms. The primary peristalsis consist of inhibition (called deglutitive inhibition) followed by excitation. The secondary peristalsis is entirely due to peripheral mechanisms and also involves inhibition followed by excitation. The lower esophageal sphincter (LES) is characterized by tonic muscle that is different from the muscle of the esophageal body. The LES, like the esophageal body smooth muscle, is also innervated by the inhibitory and excitatory neurons. The LES maintains tonic closure due to its myogenic property. The LES tone is modulated by the inhibitory and the excitatory nerves. Inhibitory nerves mediate LES relaxation and the excitatory nerves mediate reflex contraction or rebound contraction of the LES. Clinical disorders of esophageal motility can be classified on the basis of disorders of the inhibitory and excitatory innervations and the smooth muscles.

Keywords

lower esophageal sphincter; classification of esophageal motility disorders; peristalsis; neural control of peristalsis; deglutitive inhibition

INTRODUCTION

The main function of the esophagus is to transport swallowed food into the stomach. How the esophagus performs this function has been a subject of speculation and investigations for a long time. The esophagus consists of two distinct parts. In humans, the cervical and the thoracic parts of the esophagus are composed of striated and smooth muscles, respectively. The proportion of striated and smooth muscles in the esophagus differ in different animal species. Failure to appreciate that the neuromuscular apparatus and neuronal circuits for peristalsis are different in the striated and smooth muscle portions of the esophagus led to confusion and contradictions in some early studies. Experimental evidence for a swallowing center and

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sequential activation of motor neurons to elicit esophageal peristalsis was first established in the striated muscle.

The smooth muscle portion of the esophagus has myenteric plexus similar to the small intestine. However, peristalsis in the smooth muscle portion of the esophagus is very different than the intestine; the esophagus, but not intestine, can produce peristalsis at will (primary peristalsis). Therefore, peristalsis in the smooth muscle of the esophagus, as in the striated muscle of the esophagus, was also assumed to be due to sequential activation of cholinergic excitatory nerves. However, the mechanism of peristalsis in the esophageal smooth muscle turned out to be very complicated involving both central and peripheral mechanisms.

Another important function of the esophagus is to prevent gastroesophageal reflux. It has always been assumed that some kind of barrier at the gastroesophageal junction was present to prevent back flow of stomach contents into the esophagus. However, existence of a well defined lower esophageal sphincter (LES) was a matter of debate in the past. Although anatomists failed to find a well defined LES, a physiological sphincter was discovered on intraluminal pressure recordings. It was also found that the LES relaxed on swallowing. These observations stimulated investigations into the neuromuscular basis of basal tonic closure and LES relaxation associated with or unassociated with swallowing.

The purpose of this review is to present milestones in understanding of the neuromuscular mechanisms of esophageal motility and to use this understanding to develop a pathophysiological classification of esophageal motility disorders.

ESOPHAGEAL PERISTALSIS

MOVEMENT OF FOOD BOLUS THROUGH THE ESOPHAGUS

The very first scientific investigation of mechanism of food transport through the esophagus was conducted in Berlin in 1883 by a German professor, Kronecker and his medical student, Samuel Meltzer. Meltzer swallowed a balloon attached to a tube whose other end was attached a manometer to record pressure changes in the esophagus during swallowing. Professor Kronecker noted that when Meltzer swallowed a liquid bolus, the bolus was felt to enter the stomach without any pressure changes in the esophagus being recorded. Some pressure changes were noted only late in swallow. Kronecker and Meltzer[1] concluded that the tongue pumped the bolus into the esophagus which served primarily as a passive conduit for the transport of the bolus to the stomach. However, Kronecker and Meltzers' conclusion that esophagus serves only as passive conduit during gravity-assisted food bolus transport did not explain other known observations regarding the swallow-associated esophageal transport of food. For example, the esophageal transport of food to the stomach in recumbent or head down position, as in many animals and sometimes in man, remained unexplained. Ingelfinger[2] observed on fluoroscopy that swallowed barium bolus in normal volunteers in a head-down position is carried up the esophagus into the stomach by a peristaltic wave.

More recent studies of simultaneously recorded intraluminal pressures and movement of barium during a swallow resolved the apparent controversy between Kronecker and Meltzer's and Ingelfinger's findings. These studies showed that the leading edge and bulk of barium is indeed transported by gravity in the upright position. However, the tail of the liquid bolus in the upright posture, or bulk of the bolus against gravity, is propelled through the esophagus by peristaltic contraction. Thus, although barium bolus may reach the stomach soon after swallowing due to transport by gravity, it may take up to 10 minutes to complete the peristaltic sequence and complete esophageal transport of food into the stomach [3] (Fig. 1).

NEURAL CONTROL OF ESOPHAGEAL PERISTALSIS

PERISTALSIS IN THE STRIATED MUSCLE OF THE ESOPHAGUS—Since some of the early studies on peristalsis were performed in the dog, an animal species that has striated muscle throughout the esophagus, these observations apply to striated muscle of the esophagus. Doty (1954)[4] provided a comprehensive description of the swallowing reflex and motor responses of pharyngeal peristalsis. Esophageal peristalsis was thought to be similarly produced. Elegant studies in the early 1970s[5] provided electrophysiological documentation of a swallowing center in the brain stem and proposed that the central sequencing of the motor neurons in the brain stem was responsible for peristalsis in the striated muscle of the esophagus. Moreover, central mechanisms were found to be the sole pathway for peristalsis in the striated muscle of the esophagus as the existence of any peripheral mechanism of peristalsis was not found. For example, in isolated opossum esophagus *in vitro,* esophageal circular striated muscle contracted immediately upon electrical stimulation and remained contracted in a tetanic fashion during the period of stimulation. The contraction was terminated only with cessation of stimulation. *In vivo* experiments revealed that while swallowing evoked peristalsis, electrical stimulation of the vagal efferents produced non-peristaltic tetanic contractions. The central control of peristalsis in the striated esophagus is illustrated in figure 2.

PERISTALSIS IN THE SMOOTH MUSCLE OF THE ESOPHAGUS

PERIPHERAL (INTRAMURAL) MECHANISM—Once the existence of the peristalsis in the smooth muscle part of the esophagus was established, focus was shifted onto the nerves that were responsible for esophageal peristalsis. A specific issue was whether the peristalsis was a peripheral local reflex or a centrally mediated reflux. Kronecker and Meltzer had noted that the esophagus did contract during the later stages of the swallow. They had suggested that esophageal peristaltic reflux was initiated due to distension by food residues left over in the esophagus. This view was similar to the observation of peristaltic reflex in the small intestine that was described several years earlier by Bayliss and Starling (1899).[6]

The esophageal smooth muscle, unlike the striated muscle, was found to exhibit many unique responses due to the intramural nerves. The unique responses identified by Christensen in early 1970s[7,8] included: 1) the off or rebound contraction; and 2) the latency gradient. Christensen and colleagues[7] found that the circular smooth muscle of the esophagus remained quiescent during electrical stimulation but contracted only on cessation of the stimulus. They suggested that the esophageal circular muscle may actually be inhibited during the period of stimulation and subsequently contracted due to rebound phenomenon upon cessation of the stimulus. They also found that esophageal deflation following distension elicited rebound contraction. Therefore, they concluded that esophageal circular muscle contraction was a rebound following stimulation of the inhibitory nerves.

Weisbrodt and Christensen[8] also made another amazing discovery. They examined the latency of contraction to electrical field stimulation of rings of esophageal circular muscle obtained from different distances above the lower esophageal sphincter. They found that the esophageal smooth muscle rings from the most proximal part of the esophagus had the longest latency of contraction while the rings from the most distal part of the esophagus had the shortest latency of contraction. In the other rings, the latency of contraction increased from proximal to distal sites. These studies suggested that there was an inbuilt latency gradient in the wall of the smooth muscle part of the esophagus and presented a revolutionary view that local inhibitory nerves are responsible for peristalsis in the esophageal smooth muscle.

Studies from Christensen's laboratory did not identify any cholinergic excitatory nerves in esophageal smooth muscles and did not think that they were involved in peristalsis. Crist and colleagues (1984)[9] carefully examined the presence of cholinergic nerves in the esophageal

circular smooth muscle using atropine as an antagonist. They found that both cholinergic excitatory and noncholinergic inhibitory with rebound excitation responses exist in the esophageal circular muscle. [9] These responses were superimposed with short trains of electrical stimuli, but can be separated with longer stimuli, stimuli of different strengths and antagonism by atropine. They also found that cholinergic nerve stimulation act to reduce the latency of the circular muscle contraction. They also found that the degree of cholinergic and noncholinergic inhibitory influence varied at different levels of the esophagus so that cholinergic influence was most marked in the proximal parts of the esophagus and decreased distally along the esophagus.[10] On the other hand, the inhibitory nerve influence was least prominent in the proximal strips and increased distally along the esophagus. A model peripheral mechanism based on the neural gradients was presented[11] (Fig.3).

CENTRAL CONTROL OF PERISTALSIS IN ESOPHAGEAL SMOOTH MUSCLE

The fact that there was a peripheral neuromuscular mechanism that could explain peristalsis did not mean that there was no central mechanism. Swallow induced peristaltic contractions in the esophageal smooth muscle was abolished by cervical vagotomy, suggesting central control of peristalsis. However, unexpected differences in the esophageal smooth muscle to vagal efferent stimulation were found. First, cervical vagal efferent stimulation in the esophageal smooth muscle did not produce spastic contraction throughout the organ, but instead produced peristalsis similar to that elicited by swallowing.[12] These observations suggested that unlike the striated muscle, the swallowing center may provide non-sequential, simultaneous activation of the myenteric neurons and that peristalsis may be entirely due to peripheral mechanism. These observations were further supported by the fact that similar to the stimulation of intramural neurons in the muscle strips, vagal efferent stimulation also produced cholinergic (atropine sensitive) and non-cholinergic contractions depending upon the stimulus parameters.[13] It was also shown that the parameters of vagal stimulation also influenced the speed of esophageal peristalsis[14] and repeated vagal stimulation kept the esophageal muscle quiescent until the last stimulus, which was followed by peristaltic contraction.[15] This observation was similar to a previous clinical observation showing that during repeated successive swallows, the esophagus remains quiescent until the last swallow (Fig.4).

EVIDENCE FOR INHIBITION DURING THE LATENCY OF PERISTALTIC CONTRACTION

The above observations suggested but did not prove that there was actual inhibition of the muscles during the latency period of the peristaltic contraction. The inhibition of the esophageal muscle that does not have baseline contraction has been difficult to document by tension or pressure recordings. In order to document whether there was actual smooth muscle inhibition during swallow-induced peristalsis, Rattan and colleagues simultaneously recorded membrane potentials from esophageal circular muscle and intraluminal esophageal pressures.[16] They documented hyperpolarization of the smooth muscle membrane during the latency period of esophageal peristaltic contraction, suggesting that the latency period of peristaltic contraction was indeed associated with inhibition.

NATURE OF THE INHIBITORY NEUROTRANSMITTER

Murray et al. (1991) suggested that nitric oxide is the inhibitory neurotransmitter in the esophageal muscle.[17] Nitric oxide was also suggested as the inhibitory nonadrenergic, noncholinergic neurotransmitter elsewhere in the intestine.[18] Yamato and colleagues showed that nitric oxide was responsible for the latency gradient of esophageal peristalsis.[19]

The above studies established that the inhibition during the latency of peristalsis was due to vagally-activated inhibitory neurons. However, these studies do not address the possible role of vagal preganglionic fibers that may project on to the intramural cholinergic neurons.

Specifically, it was not clear whether intramural cholinergic and inhibitory neurons receive input from the same or different vagal motor fibers. To address this issue, Gidda and colleagues (Gidda and Goyal, 1984; Gidda and Goyal, 1984) recorded electrical activity from single vagal motor nerve fibers in the neck that were activated by induced swallowing.[20,21] They identified two different types of vagal fibers that could be differentiated by their characteristic discharge patterns. These two types of fibers had different latency gradients. The authors speculated that the short-latency fibers may project on to the inhibitory myenteric neurons whereas the long-latency fibers may project on to the myenteric excitatory neurons. (Fig. 5). Based on these observations, it was suggested that the inhibitory pathway consisting of short-latency vagal preganglionic fibers and myenteric inhibitory neurons in the smooth esophageal circular muscle are activated first and this is followed by peristaltic wave of excitation. Based on these observations, a model for neural regulation of esophageal peristalsis has been proposed (Fig. 5). It was also shown that either atropine and inhibitors of nitric oxide synthase could increase the speed of peristalsis by increasing the latency of contraction in the proximal esophagus and decreasing the latency of contraction in the distal esophagus, respectively.[22]

LOWER ESOPHAGEAL SPHINCTER (LES) (Fig. 6)

EARLY INVESTIGATIONS

The existence of lower esophageal sphincter has been topics of speculation for a long time. However, there was a general sense that a pressure barrier at the gastroesophageal junction must exist. Anatomists could not detect a sphincter-like structure or at least, a circular muscle thickening, at the lower end of the esophagus. The absence of any landmarks of LES made it difficult to study its morphology. Finally, manometric studies of Code and Butin[23] (Butin et. al., 1953) and Ingelfinger et al[24]. beginning in 1950s identified a high pressure zone that relaxed on swallowing, suggesting the presence of a functional LES at the gastroesophageal junction and received general acceptance. However, some specialized morphological features that characterize the LES were described.[25]

If there is a functional lower esophageal sphincter, how is its basal tone on relaxation regulated? Prevalent view at that time was that smooth muscles were innervated by the parasympathetic and sympathetic nerves and the parasympathetic nerves acted by releasing acetylcholine while the sympathetic nerves exerted their effects via the release of norepinephrine. It was thought that tonic cholinergic influence due to tonic vagal activity kept the LES closed. However, effects of vagal stimulation and vagotomy yielded contradictory and confusing results.[26] It was then proposed that may be, LES closure was due to sympathetic tonic activity. However, this proposal was also not well substantiated by studies of stimulation and sectioning of the sympathetic innervation and the enigma of the LES persisted. A kind of breakthrough occurred in early 1970s when it was proposed that it was not the tonic extrinsic nerve (vagal or sympathetic) activity that was involved in LES closure.[27] Instead, it was the tonic excitation of the intramural cholinergic neuron by circulating gastrin that kept the LES closed. However, this suggestion did not stand the test of time. So far, the mechanism of LES relaxation has remained elusive.

MYOGENIC BASIS OF LES TONE

In order to demonstrate specialized nature of the muscle at the gastroesophageal junction, Biancani and colleagues[28] performed pressure diameter curves in the LES and found that the sphincter muscle showed steeper tension-diameter curves as compared to the esophageal body muscle. Christensen et. al. (1973) generated 2 mm thick strips of the esophagus at the gastroesophageal junction. He found that these strips had mechanical properties and behavior that was different from the esophageal body circular muscle. These strips developed

spontaneous tone and had steeper length tension curves than those from the esophageal body muscles.[29]

The presence and the contribution of the myogenic tone to LES pressure *in vivo* was demonstrated by performing LES pressure by manometry, administering the sodium channel blocker tetrodotoxin and providing cardiorespiratory support to the anesthetized opossums. These studies showed that the doses that abolished neural responses in the LES did not affect LES pressure, providing strong evidence for myogenic basis of the LES tone.[30]

Subsequent studies focused on the cellular basis of myogenic tone. Asoh (Asoh and Goyal, 1978) found that the sphincter muscle shows a continuous electrical spike activity that is not seen in the esophageal body (EB).[31] Harnett et al., 2005 studied the signaling pathway for tonic contraction of LES smooth muscles.[32] Szymanski et al. (2002) reported that the composition of the contractile proteins differed in LES and EB smooth circular muscle and suggested that composition of the contractile proteins contributed to the tonic behavior of the sphincter muscle.[33]

NEURAL CONTROL OF LES

The presence of the myogenic tone allowed better assessment of excitation as well as inhibition of the LES by parasympathetic (vagus) and sympathetic nerves. Overall, the sympathetic nerves were not found to exert a major effect on LES tonic contraction and relaxation. A systematic study of the effect of vagus nerve suggested that the vagus nerve exerts a tonic inhibitory effect on the sphincter pressure so that vagotomy was found to cause LES contraction and vagal efferent stimulation caused frequency-dependent LES relaxation. The tonic cholinergic excitatory effect was demonstrated by the effect of atropine in causing basal LES hypotension and suppression of reflex contractions of the LES. It now appears that the vagus nerve provides both inhibitory and excitatory innervation to the LES.[34]

NATURE OF THE NEUROTRANSMITTERS IN THE LES

The vagal preganglionic fibers innervate the LES smooth muscle via the postganglionic myenteric neurons. The vagal preganglionic fibers to the excitatory and the inhibitory myenteric neurons are cholinergic. On the inhibitory neurons, they exert their effects via both nicotinic and muscarinic receptors. The postganglionic excitatory neurons may excite the sphincter by releasing acetylcholine and substance P. The nature of the inhibitory neurotransmitter had been elusive. Tøttrup et. al. (1991) reported that NO, as had been reported in some other gastrointestinal sphincter, may also be the inhibitory neurotransmitter in the LES[35] and Yamato (1992) showed that nitric oxide was involved in swallow-induced LES relaxation.[36] A definitive evidence for neuronal nitric oxide synthase (nNOS) as the enzymatic source of nitric oxide (NO) in LES relaxation associated with swallowing in mice was presented by Sivarao[37] (Fig. 7).

DISTINCT EXCITATORY AND INHIBITORY VAGAL PROJECTION FROM THE CNS TO THE LES

Rossiter and colleagues (1991) investigated whether the excitatory and inhibitory vagal pathways to the LES were represented by distinct preganglionic neurons in the brain stem.[38] They showed that the inhibitory and excitatory pathway preganglionic neurons were located separately in the caudal and the rostral parts of the DMV respectively. Models of distinct inhibitory and excitatory neural pathways to esophageal body smooth muscle and the LES is presented in Fig. 8.

MODULATION OF BASAL LES TONE

The myogenic tone of the LES is modulated by a variety of neurohormonal influences. Inhibitory and excitatory nerves exert a tonic influence on LES pressure *in vivo* (Fig 9). Many hormones and neurotransmitters can modify LES pressure. Nicotine, β-adrenergic agonists, dopamine, cholecystokinin, secretin, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide, adenosine, prostaglandin E, nitric oxide donors such as nitrates and inhibitors of phosphodiesterase-5 reduce LES pressure. On the other hand, muscarinic M2 and M3 receptor agonists, α-adrenergic agonists, gastrin, substance P, and prostaglandin $F_{2\alpha}$ cause LES contraction.

LES REFLEXES

SWALLOW-ASSOCIATED LES RELAXATION—The LES response to swallowing consists of relaxation of the LES tone, which is followed sometimes by a rebound contraction. The monitoring of the LES relaxation requires avoidance of the artifacts related to the movement of the abdominal esophagus into the chest. The relaxation starts within seconds of swallowing and lasts 5 to 8 minutes. The relaxation is part of the deglutitive inhibition and is mediated by the vagal inhibitory pathway and the postganglionic myenteric neurons that act by releasing nitric oxide.

ISOLATED LES RELAXATION

Relaxation of the LES without esophageal peristalsis may occur during belching, vomiting and the so-called transient LES relaxation (TLESR) (Fig. 10).[39] TLESRs are evoked by gastric distension and stimulation of abdominal vagal afferents. Sang and colleagues investigated brain stem neurons involved in isolated LES relaxation and swallow reflex.[40,41] Isolated LES relaxation is a vagovagal reflex that involves only the inhibitory pathway (Fig. 11). This is in contrast to swallow reflex that involves both inhibitory and excitatory pathways. Reflex LES relaxation is augmented by phosphodiesterase-5 inhibitors such as sildenafil that increase cyclic guanosine monophosphate (cGMP) in the sphincter muscle, and is inhibited by GABA-B agonists such as baclofen.

DIAPHRAGMATIC PINCHCOCK

In addition to the role of LES, the role of the diaphragmatic pinchcock that forms the esophageal hiatus in the diaphragm as an antireflux barrier has been a subject of considerable debate in the past. More recently, Mittal et. al. (1988) have systematically investigated the role of the diaphragmatic pinchcock and has suggested that the striated muscle of the diaphragmatic crural fibers that surrounds the LES acts as an external LES.[42]

ARE THE CONCLUSIONS REGARDING ESOPHAGEAL PHYSIOLOGY IN EXPERIMENTAL ANIMALS APPLICABLE IN HUMANS?

Most of the studies that require invasive experimental protocols have been performed in experimental animals. Studies in dogs and rodents generally provide information on the esophageal striated muscle and studies on the opossums and to some extent cats have provided information on the smooth muscle of the esophagus. The lower esophageal sphincter in dogs and rodents is also a smooth muscle structure. The doubt remains whether the observations in experimental animals are applicable to humans. Invasive studies performed on experimental animals are not possible or appropriate in humans. However, models on the basis of experimental studies have been tested in humans. In general, no significant differences between animal and human physiology has been found. However, it has been suggested that cholinergic influences may be more prominent in human smooth muscle than in the opossum esophagus.

PATHOPHYSIOLOGICAL CLASSIFICATION OF ESOHAGEAL MOTILITY DISPORDERS

Esophageal motility disorders can be classified based on pathophysiology depending upon the involvement of one or more of the three control mechanisms of esophageal motility, namely, inhibitory innervation, excitatory innervation and the smooth muscles (Figure 12). The inhibitory pathway is responsible for the gradient of peristaltic contraction in the esophageal body and relaxation of the LES. Deficiency of inhibitory innervation may lead to achalasia and diffuse esophageal spasm (DES). In achalasia, both the LES and esophageal body are affected whereas in DES, esophageal body is primarily affected. On the other hand, increased inhibitory nerve reflex is responsible for the so-called TLESR. In contrast, impairment of the excitatory nerves may lead to hypotensive peristaltic contractions and hypotensive LES and gastroesophageal reflux disease. Over-activity of the excitatory nerves may lead to increased force of esophageal peristaltic contractions, LES basal hypertension and hypertensive contraction. Smooth muscle disorders may also affect the force of peristaltic contraction and LES tone. Myogenic weakness, for example in scleroderma, may lead to hypotensive peristalsis and hypotensive LES. Myogenic hyper-excitability may be the basis of hypertensive peristalsis and hypertensive LES.

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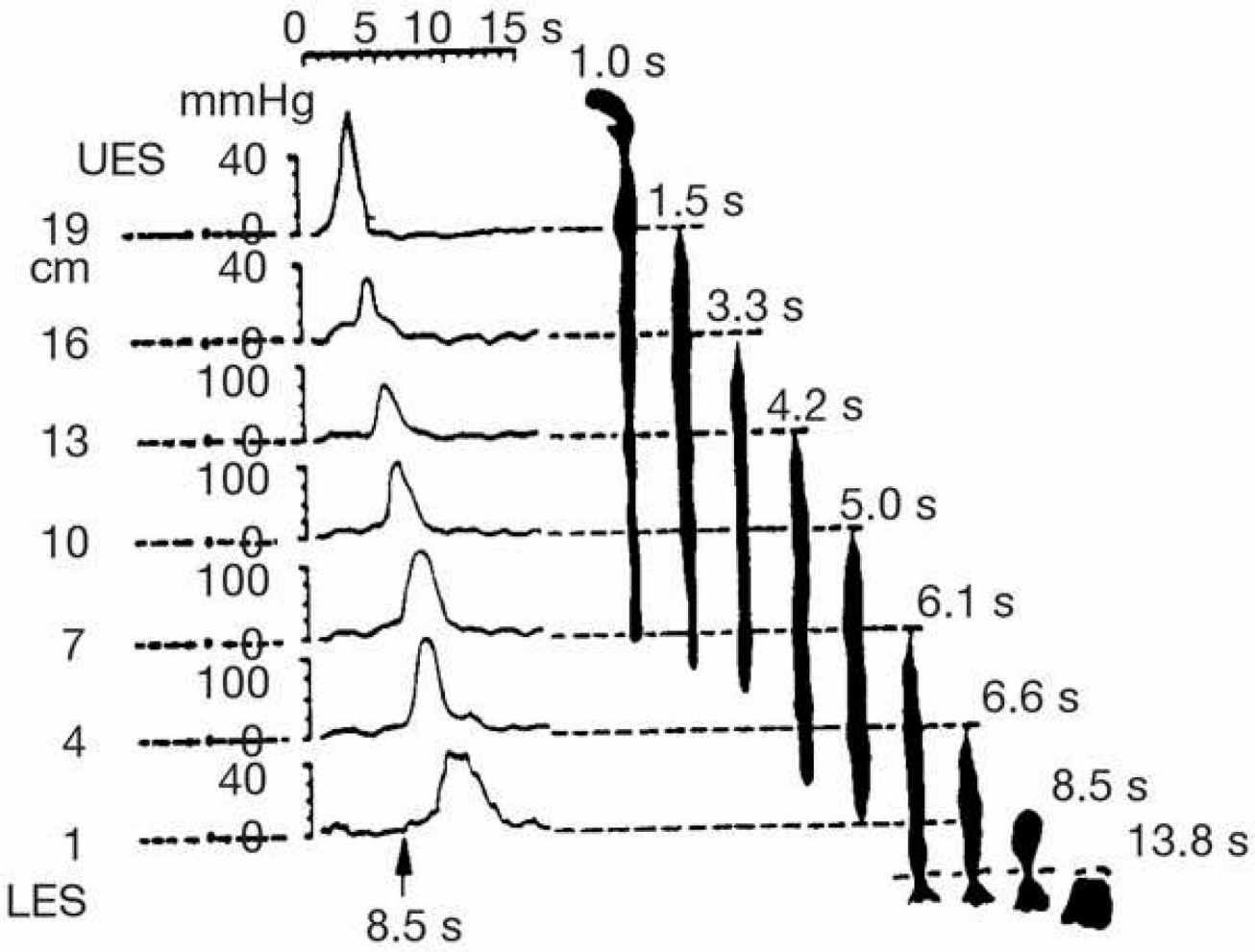

Figure 1. Simultaneous esophageal manometry and fluoroscopy

Note that, on swallowing, the barium column moves down the esophagus. Such barium movement in the upright position occurs largely due to gravity. The tail of the barium column moves down the esophagus by the esophageal peristaltic contraction. Note that barium moves through the esophagus in its relaxed state. Also note that onset of peristaltic contraction at lowest level of the esophagus occurred at 8.5 sec after a swallow, at which time the entire column of barium passes into the stomach. (Source: Modified from Dodds WJ, Christensen J, Dent J, Arndorfer RC, Wood JD. Pharmacologic investigation of primary peristalsis in smooth muscle portion of opossum esophagus. Am J Physiol 1979;237(6):E561–E566 and Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo3, 2006).

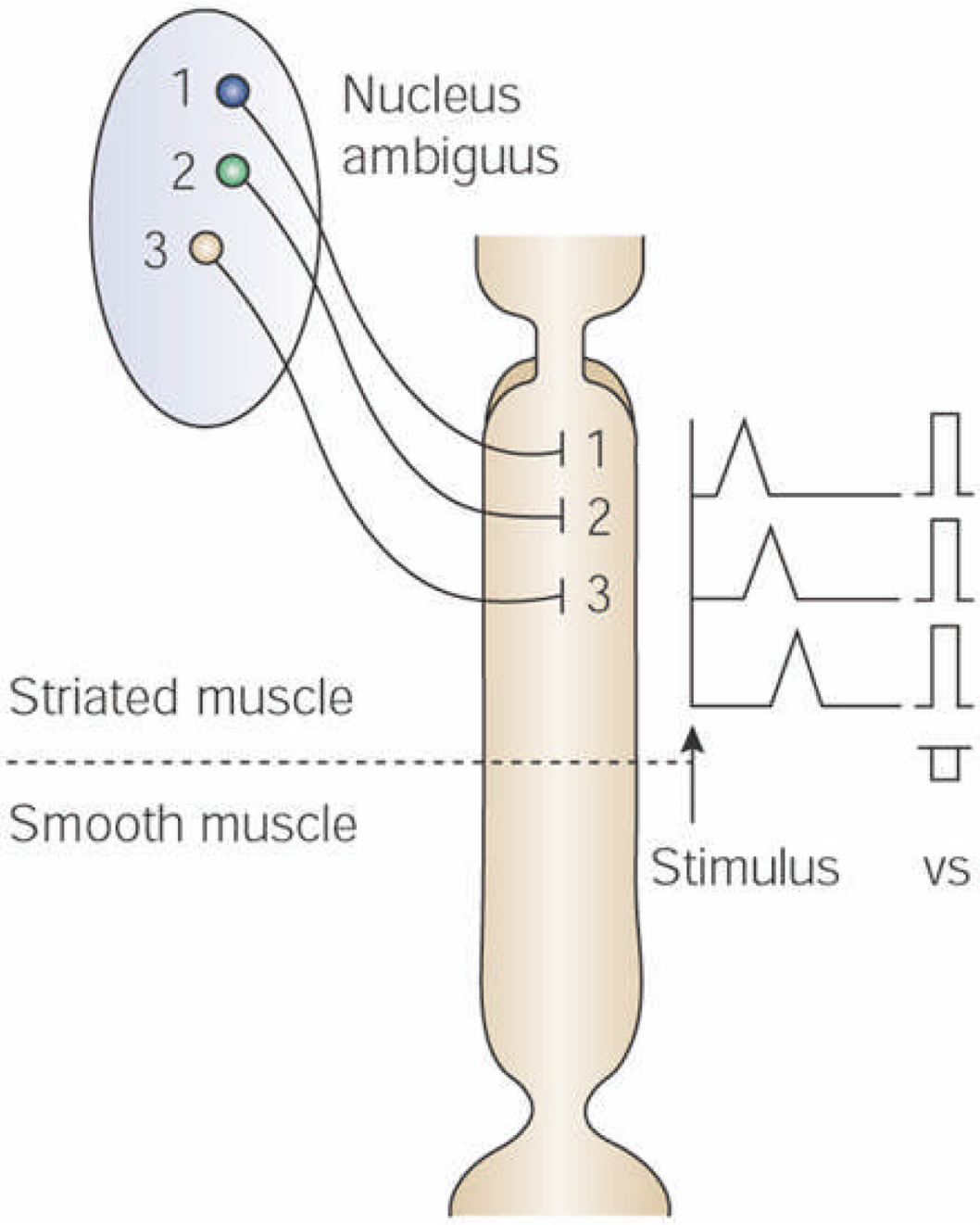

Figure 2. A model of peristalsis in the striated muscle of the esophagus

Note that swallow-induced peristalsis is due to sequential activation of lower motor neurons in the nucleus ambiguus in the brainstem. When the peripheral end of the decentralized vagus nerve is electrically stimulated (VS), all segments of the esophagus contract simultaneously. (Source: Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo3, 2006).

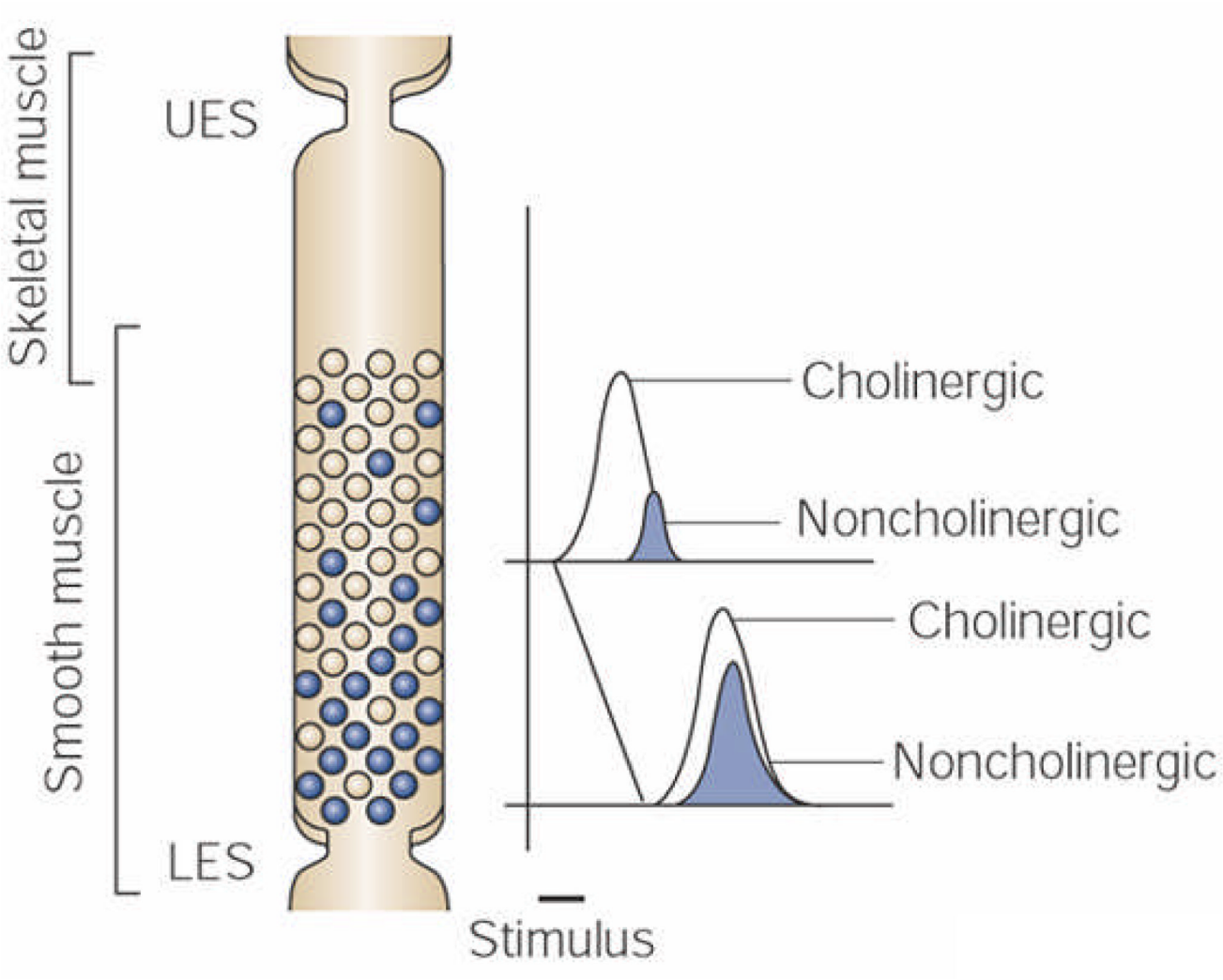

Figure 3. A model of intramural mechanism of peristalsis in the esophageal smooth muscle

The cholinergic excitatory innervation (open circles) is most marked in the proximal part and decreases gradually in the distal part. On the other hand, the inhibitory innervation (close circles) increases distally along the esophagus. Upon stimulation of the inhibitory nerves alone, the latency of contraction increases gradually distally along the esophagus, resulting in peristaltic sequence of contraction that is entirely located locally in the wall of the esophagus. However, cholinergic nerves further reduce the latency, particularly in upper levels of the esophagus because of their greater influence in the upper esophagus. (Source: Crist J, Gidda JS, Goyal RK. Intramural mechanism of esophageal peristalsis: roles of cholinergic and noncholinergic nerves. Proc Natl Acad Sci USA 1984; 81(11):3595–3599 and Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo3, 2006).

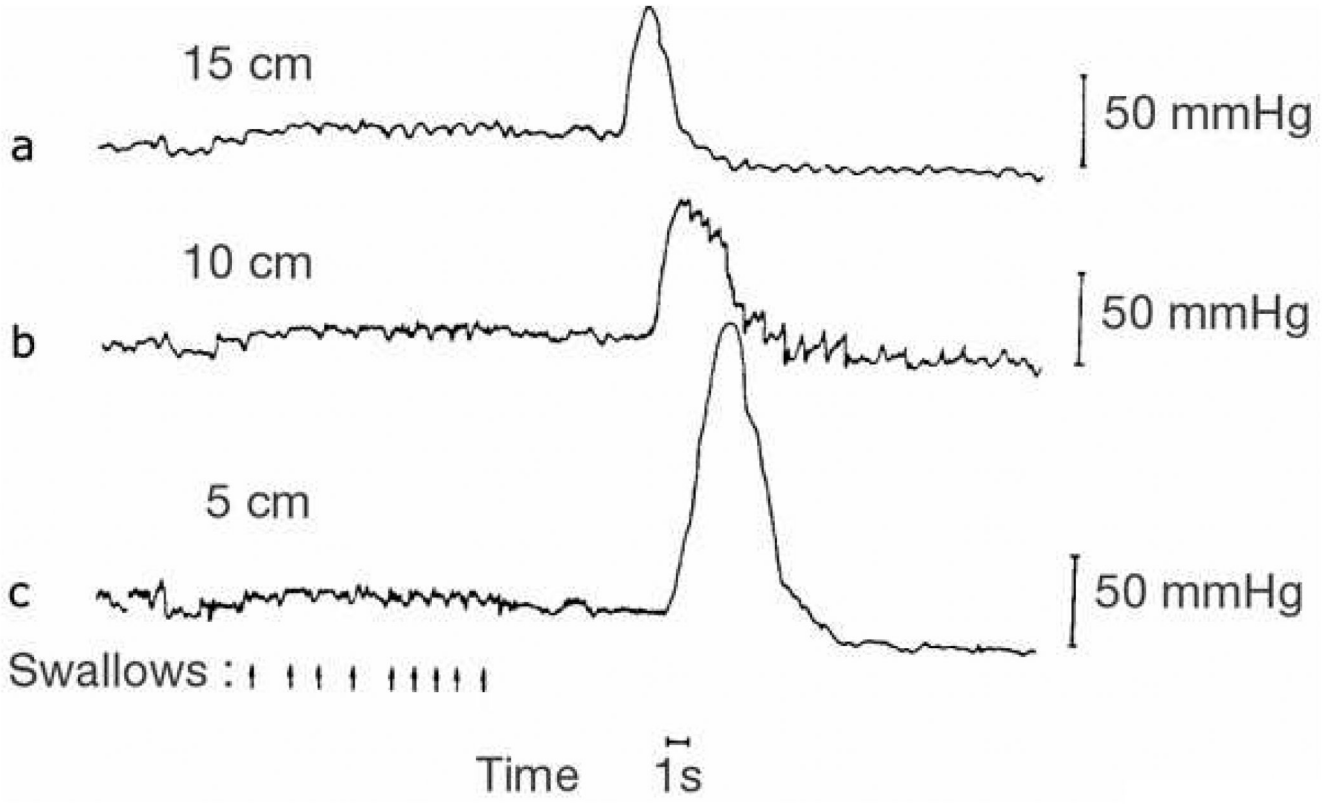

Figure 4. Demonstration of deglutitive inhibition on successive rapid swallowing (as in rapid drinking) in a health volunteer

Note that the subject was making repeated swallows every 1 to 2 seconds. During the swallows, there was no activity in the esophagus. The last swallow was followed by a peristaltic contraction.(Source: Ask P, Tibbling L Effect of time interval between swallows on esophageal peristalsis. Am J Physiol. 1980 Jun;238(6):G485-90 and Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi: 10.1038/gimo3, 2006).

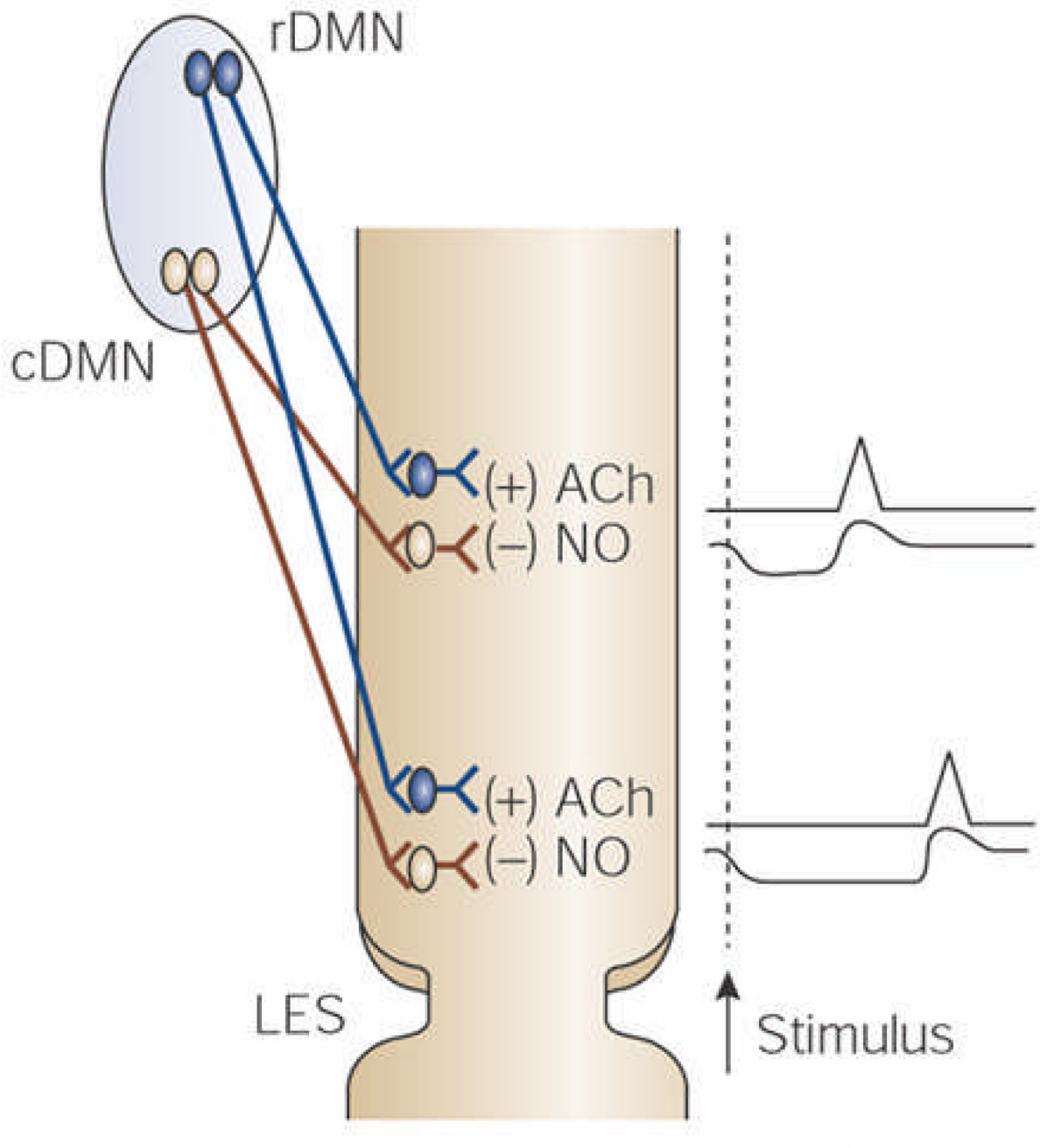

Figure 5. A model of neuromuscular organization of smooth muscle of esophageal body and the LES

The innervations of the esophageal body and LES are similar. The excitatory pathway includes vagal preganglionic neurons that are located in the rostral part of the DMN in the brainstem. These fibers project onto the excitatory postganglionic neurons that contain acetylcholine (ACh) and substance P. The inhibitory pathway includes pre-ganglionic vagal fibers that are located in the caudal part of the DMN. These fibers project onto postganglionic inhibitory neurons that contain nitric oxide (NO), vasoactive intestinal polypeptide (VIP) and adenosine triphosphate (ATP). However, as the esophageal body (EB) muscle is phasic in nature, it does not exhibit resting tone and contracts transiently upon nerve stimulation with a certain latency.

On the other hand, the lower esophageal sphincter (LES) muscle is tonic in nature; it exhibits basal tone and initially relaxes on intramural nerve stimulation. (Source: Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo3, 2006).

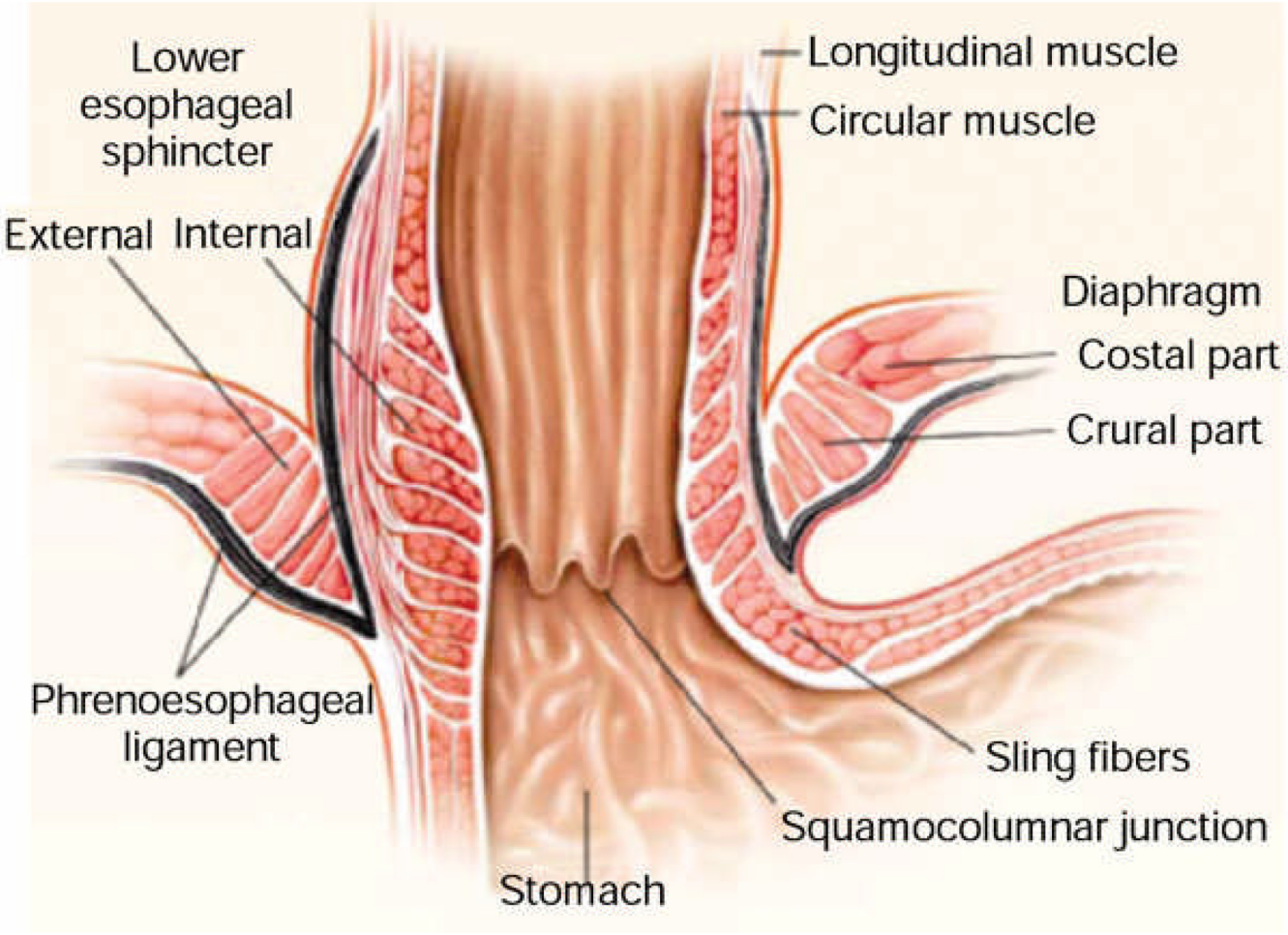

Figure 6. A model of central control of peristalsis in the smooth muscle esophagus

The inhibitory and excitatory pathway neurons (cell bodies) to the esophageal smooth muscle are segregated in the caudal and rostral parts of the dorsal motor nucleus of the vagus. Upon swallowing, the inhibitory pathway neurons in the caudal DMN (cDMN) are activated first, which causes simultaneous inhibition of all parts of the esophagus. This inhibition lasts longer in the lower than in the upper parts. As the inhibition ends, sequential activation of excitatory (cholinergic) neurons in the rostral DMN (rDMN) elicits a contraction wave that is combined with the rebound peristaltic wave. (Source: Ravinder K. Mittal and Raj K Goyal, Sphincter mechanisms at the lower end of the esophagus. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo14, 2006).

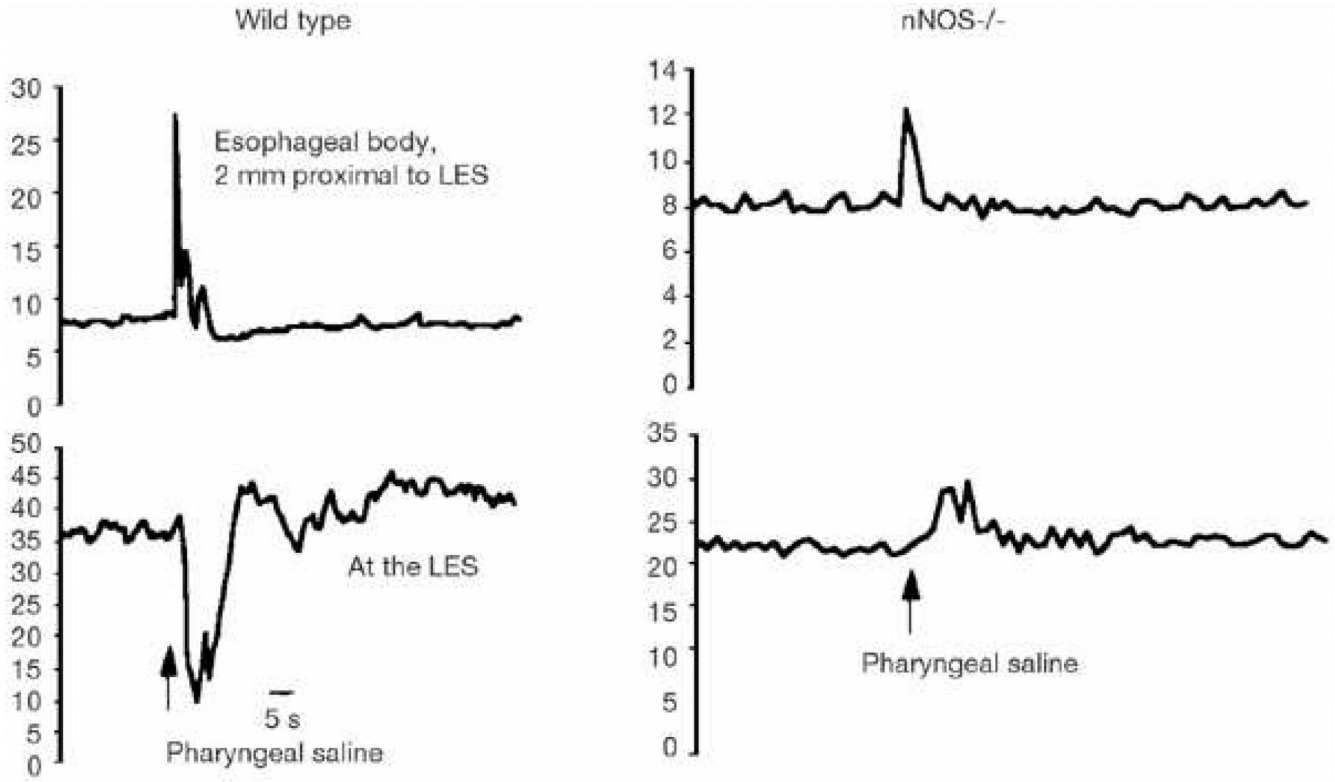

Figure 7. Diagrammatic presentation of the lower esophageal sphincter and the crural diaphragm that constitute the intrinsic and extrinsic sphincters

The two sphincters are anatomically superimposed on each other and are anchored by the phrenoesophageal ligament. (Source: Mittal RK, Balaban DH. The esophagogastric junction. N Engl J Med 1997;**336**:924–932 and Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo3, 2006).

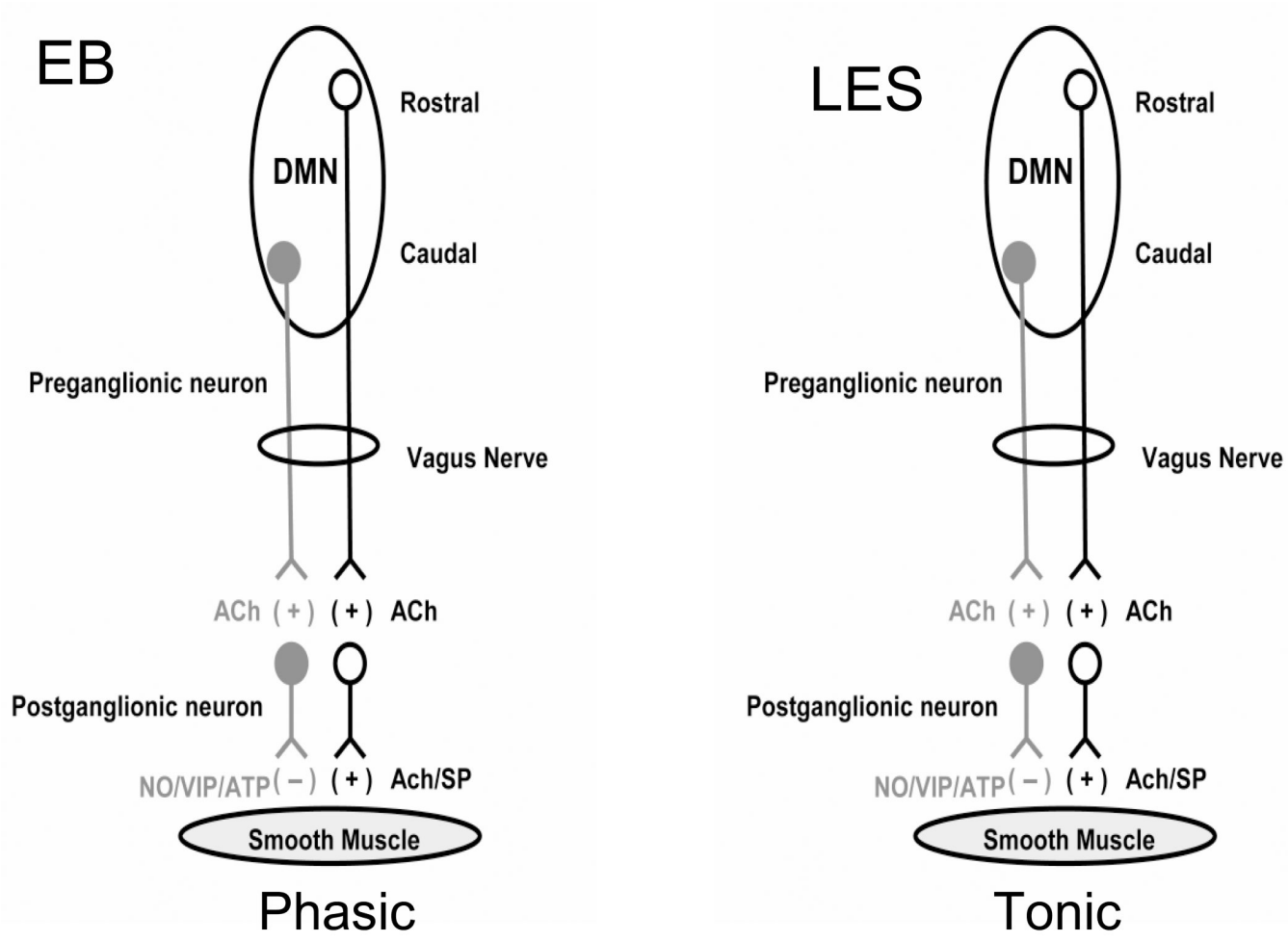

Figure 8. A model of regulation of basal LES tone

Basal LES pressure is dependent on three factors: 1) myogenic tone; 2) inhibitory nitrergic nerves; and 3) excitatory cholinergic nerves. The effect of inhibitory and the excitatory nerves is normally counteracted. The loss of all nerves may not decrease LES pressure, the loss of inhibitory nerves may cause transient LES hypertension and the loss of the cholinergic excitatory nerves may cause transient LES hypotension. EB, esophageal body; LES, lower esophageal sphincter.

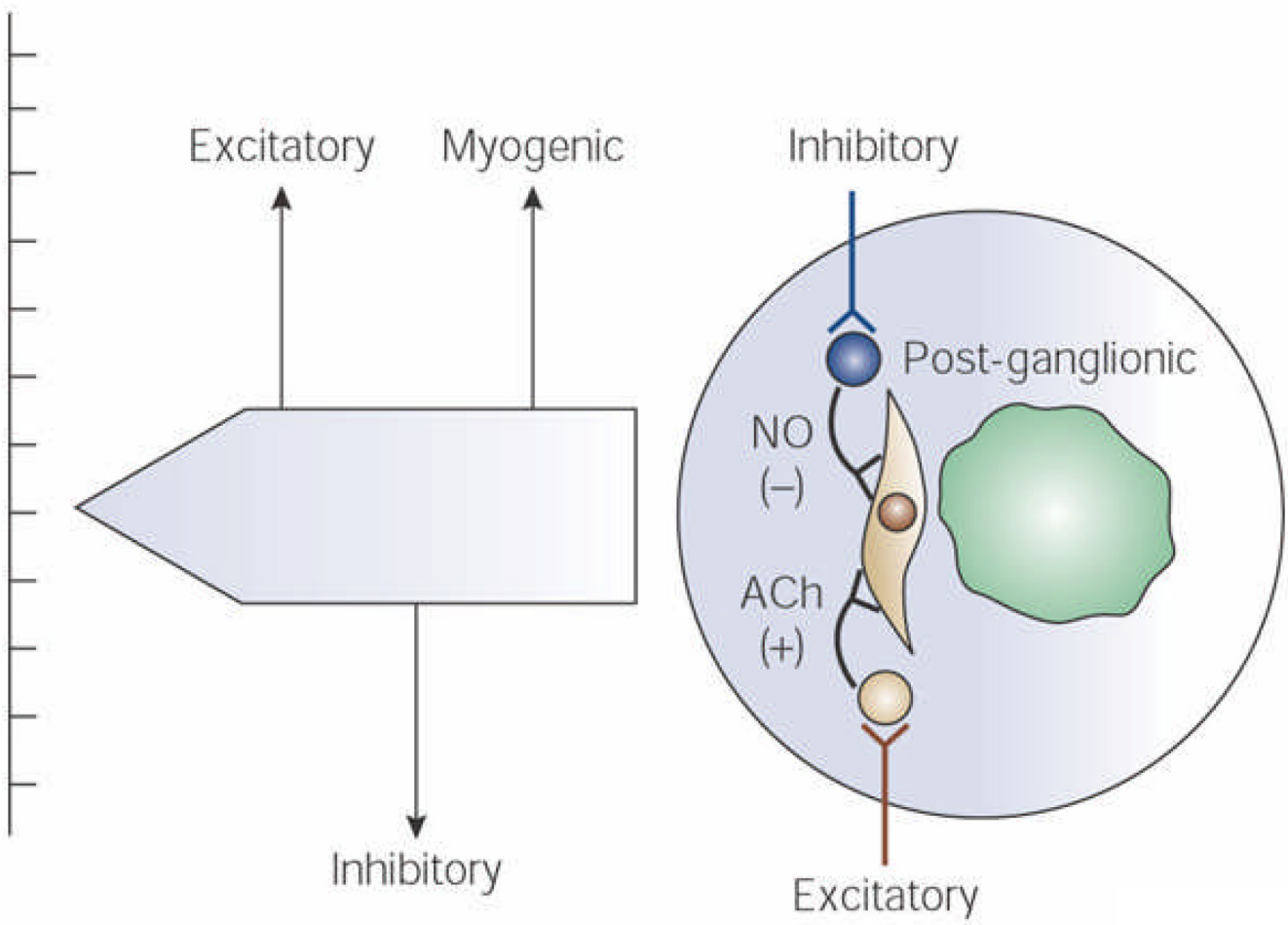

Figure 9. Loss of LES relaxation to a swallow in neuronal nitric oxide synthase (nNOS) deficient but not in the wild type mice

These studies established that nNOS is the enzymatic source of nitric oxide involved in the inhibitory neurotransmission (Source: Sivarao, DV, Mashimo, HL, Thatte HS and Goyal RK. Lower esophageal sphincter is achalasic in nNOS−/− and hypotensive in W/Wv mutant mice. Gastroenterology 200l; 121:34–42 and Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo3, 2006).

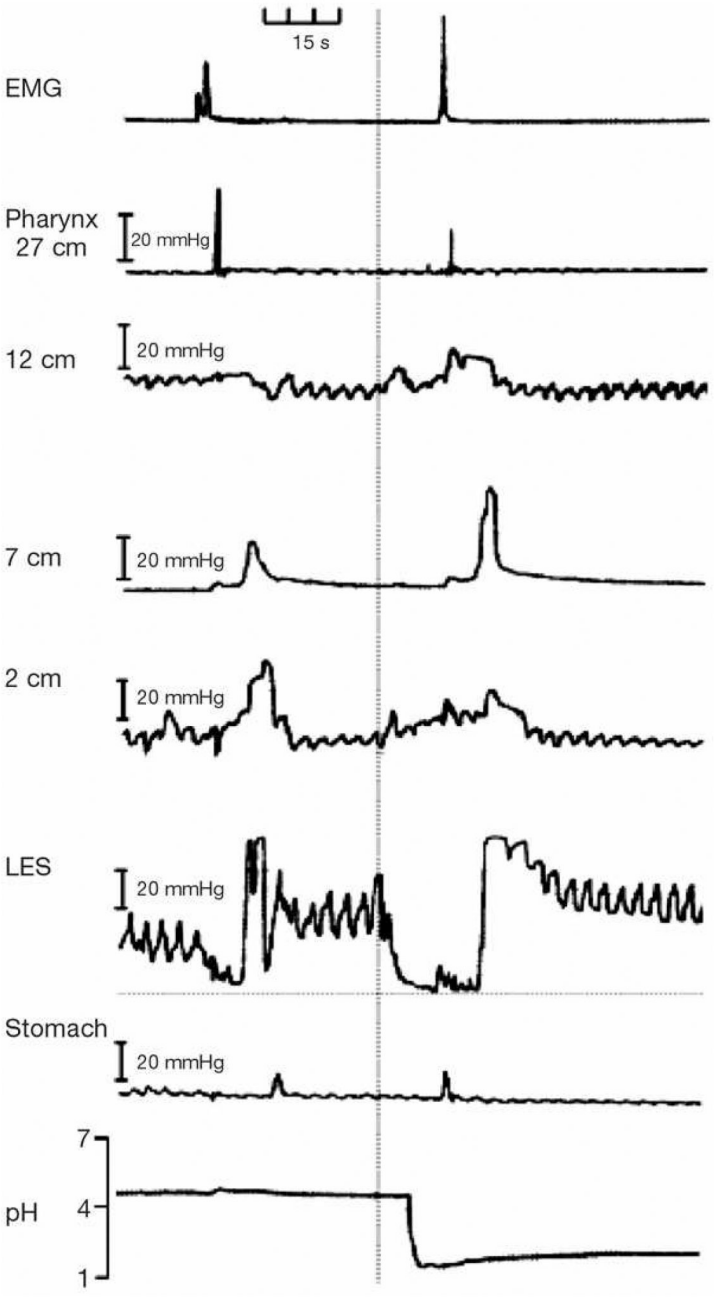

Figure 10. An example of so-called transient LES relaxation (TLESR)

Note the swallow associated events, including submental EMG activity, pharyngeal contraction, and esophageal peristaltic contraction. Also note TLESR-associated events, including the lack of submental EMG activity and the lack of pharyngeal or esophageal peristalsis. Also note the TLESR that is associated with a brief esophageal contraction and fall in esophageal pH from 5 to 1. The TLESR is of longer duration than swallow-induced LES relaxation. (Source: Mittal RK, McCallum RW. Characteristics of transient lower esophageal sphincter relaxation in humans. Am J Physiol 1987; 252:G636–G641 and Ravinder K. Mittal and Raj K Goyal, Sphincter mechanisms at the lower end of the esophagus. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo14, 2006).

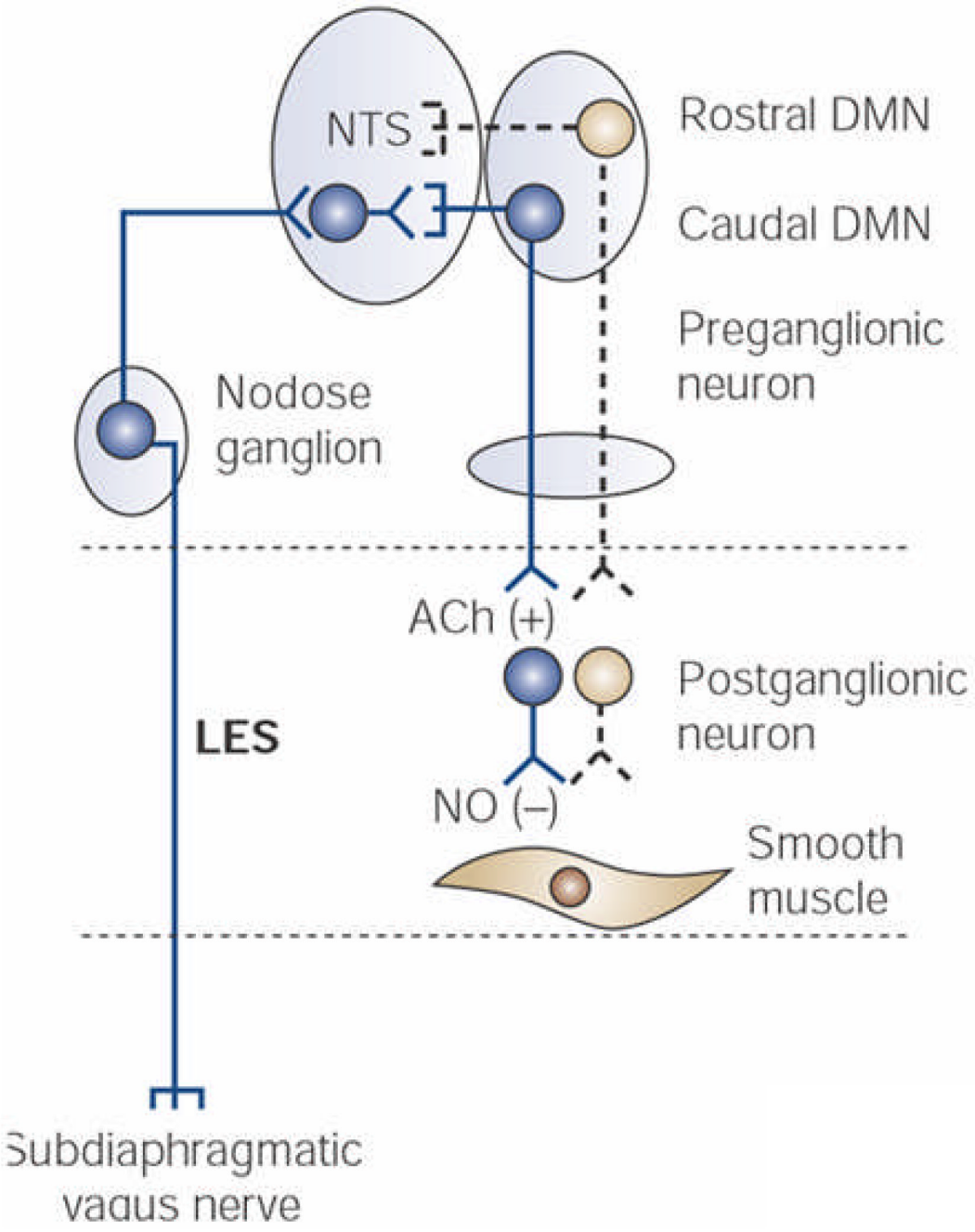

Figure 11. A model of neural pathway for TLESR

The subdiaphragmatic vagal afferents arising from the stomach project on to the nucleus tractus solitarius (NTS). The NTS neurons connect with neurons of the inhibitory pathway in the caudal part of the DMN. The inhibitory pathway neurons in the DMN mediate relaxation via nitrergic neurons. This is in contrast to swallow induced relaxation that is accompanied by slightly delayed activation of the excitatory motor neurons. (Source: Goyal RK, Padmanabhan R, Sang Q. Neural circuits in swallowing and abdominal vagal afferent-mediated lower esophageal sphincter relaxation. Am J Med. 2001; 111 Suppl 8A:95S–105S and Hiroshi Mashimo and Raj K Goyal. Physiology of esophageal motility. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo3, 2006).

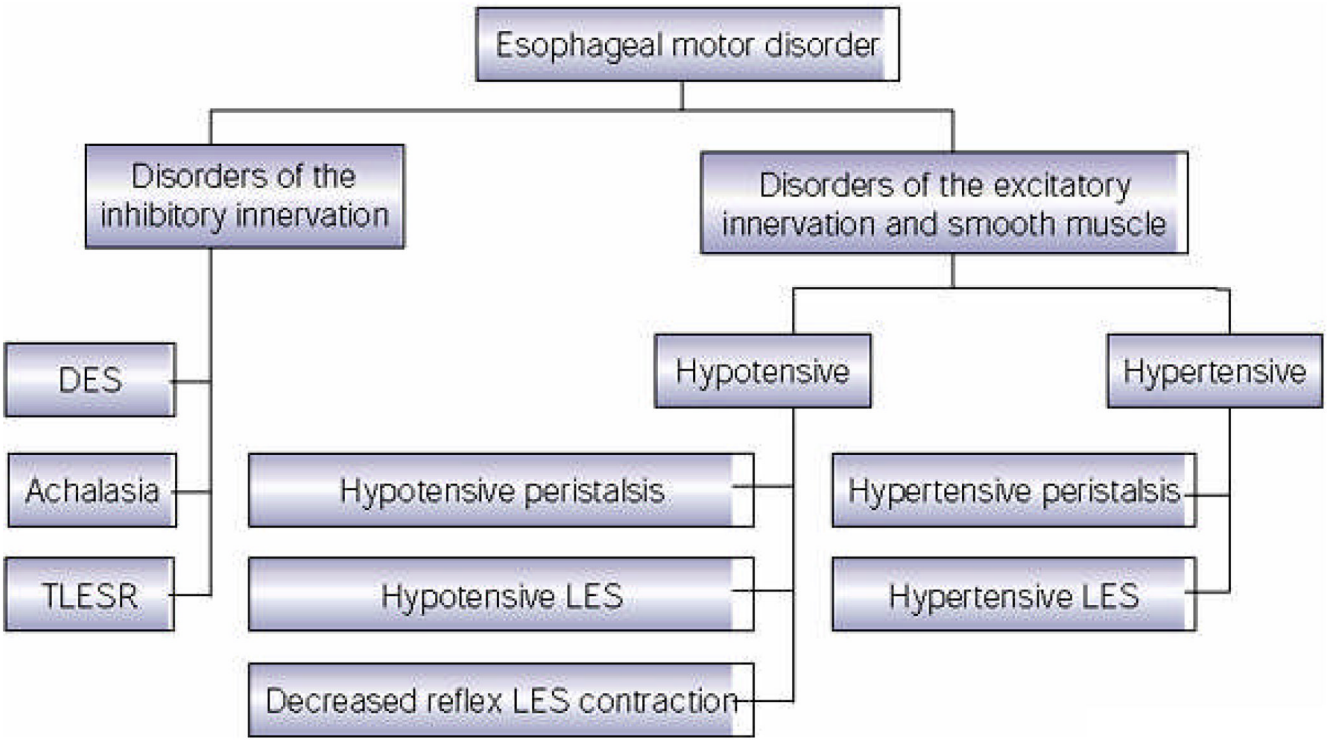

Figure 12. Classification of esophageal motility disorders based on pathophysiology

The esophageal smooth muscle motility disorders can be classified based on involvement of one or more of its three components, namely, inhibitory nerves, excitatory nerves and smooth muscle. Note that the loss of inhibitory innervation leads to achalasia involving LES and EB and diffuse esophageal spasm (DES) involving only esophageal body. These and related conditions are characterized by loss of the deglutitive inhibition and latency gradient. Over-activity of the inhibitory TLESR may lead to gastroesophageal reflux disease (GERD). On the other hand, impairment of cholinergic excitatory innervation leads to hypotensive LES leading to GERD, and hypotensive peristalsis. Similarly, impairement of myogenic contractile activity also leads to hypotensive LES and GERD, and hypotensive peristalsis. Severely hypotensive peristalsis also causes dysphagia. Hypertensive LES and hypertensive peristalsis (nutcracker esophagus) may be due to over-activity of the excitatory nerves or myogenic hyper-excitability. (Source: W.G. Patterson, Raj K Goyal and Fortunée Irene Habib, Esophageal motility disorders. GI Motility Online, www.GIMotilityonline.com; doi:10.1038/gimo20, 2006).