

Review Article

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Function of the esophageal mechanoreceptors

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Introduction

There have been many review articles of the anatomy, histology and sensory nature of the esophageal mechanoreceptors, but none have also fully reviewed the functions of these receptors [1-6]. There were three basic types of studies used to define the esophageal mechanoreceptors and their functions: a) histological studies, which identified and localized possible mechanoreceptors [7-16], b) physiological studies which defined the afferent neural responses of mechanical stimulation of the esophageal wall [15-21], and c) physiological studies which defined the reflex effects of mechanical stimulation of the esophageal wall [6,10,22-49]. While these studies identified and characterized the esophageal mechanoreceptors or identified the

Abstract

There are four histologically defined esophageal mechanoreceptive agents with evidence-based functions, three are mechanoreceptors and one is a mechanoreceptive inhibitory afferent nerve. The slowly-adapting tension sensitive receptors of the esophageal myenteric plexus function to prevent Esophago-Pharyngeal Reflux (EPR) through the Esophago-Upper Esophageal Sphincter Contractile Reflex (EUCR), Esophago-Esophageal Contractile Reflex (EECR), and Secondary Peristalsis (SP). The rapidly-adapting touch sensitive receptors of the esophageal mucosa function to promote EPR and airway protection during belching through esophago-upper Esophago-Upper esophageal sphincter Relaxation Reflex (EURR), Esophago-Glottal Closure Reflex (EGCR), Esophago-Hyoid Distraction Reflex (EHDR), and Esophageal Retrograde Peristaltic Reflex (ERPR). The slowly-adapting tension receptors of the mucosa function to promote bolus transport from pharynx to stomach by activating the Esophago-Pharyngeal Swallow Reflex (EPSR) instead of SP, especially in infant humans and animals, and ensuring that the esophageal phase of swallowing follows the pharyngeal phase. The afferent receptive inhibitory motor neurons innervating the LES and crural diaphragm function to eliminate the esophago-gastric barrier, i.e., LES and crural diaphragm contraction, during swallowing and belching. There are also undefined mechanoreceptors of the esophagus which activate splanchnic nerve afferents and probably mediate autonomic and nociceptive functions. However, the specific receptors as well as responses involved have not been identified.

neural or physiological effects of various esophageal stimuli, there were none that had defined esophageal mechanoreceptors and their functions in the same experiments. Therefore, for this review histological studies were analyzed first to identify the known mechanoreceptors, and the other studies were used to apply the appropriate reflex responses and functions to each mechanoreceptor.

Esophageal mechanoreceptors

Slowly adapting muscular mechanoreceptors

The first esophageal mechanoreceptor observed using histological techniques [7,12,13] was the receptor of the myenteric

plexus which was described as an Intraganglionic Laminal Ending (IGLE [12,13]). Independent structures within the ganglia, which have spindle shaped thickenings towards their endings, are mostly found in the upper and lower portions of the esophagus and make contact with the vagus nerve [7]. These characteristics suggested that these structures are sensory in function and probably mechanoreceptive [7,12,13]. Later studies [16] found that either contraction or distension of the esophagus activated the IGLE's of the myenteric plexus, thereby defining them as mechanoreceptors.

The first step to identifying the function of this mechanoreceptor was defining its response characteristics and sensory innervation. It was found that applying tension to the esophageal wall by inflating a balloon intraluminally activated vagal afferents and did this in a slowly-adapting manner [8,11,16-22]. That is, the rate of vagal response was directly related to the magnitude of the tension applied to the esophagus and did not stop responding until the tension stopped. Other types of stimuli, like stroking the mucosa, had no effect on this receptor [8,19,20]. Therefore, this myenteric plexus mechanoreceptor was innervated by vagal afferents and operated in slowly-adapting manner.

It was found that distension or contraction of the esophagus [24,29,32,35] was associated with contraction of the esophagus orad of the stimulus (Esophago-Esophageal Contractile Reflex (EECR)) and/or the upper esophageal sphincter (Esophago-UES Contractile Reflex (EUCR)), and usually followed by Secondary Peristalsis (SP). The most significant study [30] associating the slowly-adapting muscular mechanoreceptor with these reflexes was the observation that removal of the mucosal layer of the esophagus blocked all reflexes stimulated by distension of the esophagus except the EUCR, EECR, and SP (Figure 1). Considering that no other receptor had been found in the muscular layer or that anesthetizing the mucosa with lidocaine did not block SP or EUCR [30], these reflexes must have been mediated by muscular mechanoreceptors. This was further confirmed by the observations that the EUCR and SP were more readily activated by a slowly rather than rapidly applied tension to the esophageal wall and that these reflexes were not activated by stroking the esophageal mucosa [30]. Therefore, the slowly-adapting muscular mechanoreceptor mediates EUCR, EECR, and SP.

The functions of EUCR, EECR and 2P are complimentary, and when acting together unified. The EECR acts to block or inhibit the orad movement of any esophageal bolus orad of the stimulus [35], the EUCR acts to prevent esophago-pharyngeal reflux of the bolus [30] and SP acts to move distally a bolus orad of the stimulus [3,6]. Therefore, since all three reflexes are activated by the same stimulus in the same region of the esophagus [30], these three reflexes have a unified function of preventing any bolus remaining in the esophagus after the passage of peristalsis to be refluxed to the pharynx.

Rapidly adapting mucosal mechanoreceptors

The first study suggesting that there was a receptor in the mucosa of the esophagus found intraepithelial fibers lining the wall within the mucosa [14]. This location and structure suggested that they had a sensory function. It was later found that this mucosal receptor is a vagally mediated mechanoreceptor [17,18], but the specific nature of the stimulus activating this

receptor was identified later. In later more controlled studies [8,19,20], it was found that the vagally mediated mechanoreceptors of the esophageal mucosa are best stimulated by stroking the mucosa, rather than applying tension to the esophageal wall. In addition, it was found that these mechanoreceptors are rapidly-adapting [8,19,20], that is, the primary response is at the beginning or ending of the stimulus, and they respond best to a rapidly applied stimulus.

The function of these rapidly-adapting mucosal mechanoreceptors was defined by experiments which investigated the effects of removal of the mucosa from the esophagus. It was found that removal of this layer of the esophagus totally eliminated the activation of belching [30] and the reflex effects that occur during belching, but had no effect on EUCR, EECR or SP (Figure 1). These belch-related reflexes [30,34,50] are esophago-upper esophageal sphincter (UES) relaxation reflex (EURL) (Figures 1, 3, 4 & 6), Esophago-Glottal Closure Reflex (EGCR) (Figures 1 & 2), Esophago-Hyoid Distraction Reflex (EHDR) (Figures 1 & 3), and the Esophageal striated muscle Retrograde Peristaltic Response (ERPR) (Figure 4). Belching and all of these associated reflexes are activated by rapid injection of air into the esophagus [30,34,50], which correlates very well with the rapidly-adapting nature of the mucosal mechanoreceptors. In addition, belching and all of these reflexes are mediated by the vagus nerve [30,34], which is the afferent nerve of the rapidly-adapting mucosal mechanoreceptors. Therefore, the rapidly adapting mucosal mechanoreceptors mediate belching and its associated reflexes, which aid the process: EURL, EGCR, EHDR and ERPR.

Slowly adapting tension/mucosal mechanoreceptors

In one early study [15] esophageal mechanoreceptors were identified by recording responses from vagal afferent fibers innervating the cervical esophagus during esophageal contraction or respiration. One set of receptors acted like the slowly-adapting muscular tension receptors, but a second set activated by esophageal distension exhibited responses which had characteristics of both slowly-adapting and rapidly-adapting mechanoreceptors. That is, at the beginning of the distension the receptor was maximally activated and this response declined even though the stimulus did not, similar to a rapidly-adapting receptor. The response of the receptor then acted like a slowly-adapting receptor as the rate of the response was directly related to the strength of the distension [15]. In later more detailed studies [20], it was found that there are slowly-adapting tension mechanoreceptors in the mucosa, which also respond to touch [20].

The function of the mucosal slowly-adapting tension mechanoreceptors has not been defined, but there are two studies which strongly suggest a function. Stimulation of the Esophagus can activate the Pharyngeal Swallow (EPSR) (Figure 5), but this response is more sensitive in animals [33] and infant humans [51,52] than adult humans [59]. In cat studies [33], it was found that the EPSR is activated in a probabilistic manner. That is, the larger the bolus, the longer area of the esophagus stimulated, and the closer the stimulus is to the UES, the more likely it is for the stimulus to activate the pharyngeal swallow. The EPSR [33] was blocked by lidocaine applied to the esophageal mucosa, and intraluminal injection of HCl into the esophagus increased the probability of activation of EPSR [33]. These studies suggested that the EPSR is activated by stimulation of receptors

in the mucosa of the esophagus. Considering that the EPSR is not secondary peristalsis, secondary peristalsis is mediated by muscular mechanoreceptors [30], the EPSR is activated by tension to the esophageal wall [33], and EPSR [33] but not SP [53], is blocked by luminal application of lidocaine, it was concluded that the EPSR is mediated by the slowly-adapting tension mechanoreceptors of the esophageal mucosa [33].

The physiological function of the EPSR was hypothesized to be a mechanism which guaranteed bolus transport during swallowing, thereby, preventing aspiration [33,54]. The EPSR is most sensitive in animals [33,54] and infant humans [51,52], and in both the larynx is high in the neck [55]. This high position allows the epiglottis to go behind the soft palate and the larynx to open directly into the nasopharynx [56]. If a swallowed bolus gets stuck in the upper esophagus and secondary peristalsis is activated, this contraction of the upper esophagus could push the bolus orad as well as caudad and cause esophago-pharyngeal reflux and aspiration. However, if instead of activating secondary peristalsis, the pharyngeal swallow is activated this response would push the bolus down the esophagus without any possibility of reflux or aspiration [56]. This scenario of esophageal reflux in human infants is not unreasonable or unlikely as esophageal reflux induced aspiration is the primary theory accounting for sudden infant death syndrome [54,57,58].

Another way in which the mucosal slowly-adapting tension mechanoreceptors function to promote bolus transport is by ensuring that the esophageal phase of swallowing follows the pharyngeal phase. It has been observed in various species [30,60,61] that diversion of the swallowed bolus from the esophagus prevents the initiation of the esophageal phase of swallowing (Figure 6). This occurs not only for swallows with a bolus, but also for non-bolus swallows [30]. Given that the receptor of this function must be very sensitive and close to the mucosal surface, it is highly likely that activation of the mucosal slowly adapting tension receptors mediates this function. Therefore, the mucosal slowly adapting tension mechanoreceptors of the esophagus activate two reflex responses that function to promote the transmission of the swallowed bolus from pharynx to stomach and prevent aspiration.

Mechanosensitive esophageal inhibitory motor innervation

There is one more receptive process of the esophagus that alters physiologic function, but it is not through a separate unique receptor, it is through inhibitory motor nerves with receptor properties [10,23,25,29,36,37]. Unlike the esophageal mechanoreceptors described above, the function of this receptive process was identified and characterized before the receptive process [10,23,25,29,36,37].

The first indication of this receptor was in the studies which found that stretching or contraction of the distal esophagus caused the Lower Esophageal Sphincter (LES [23,25] and crural diaphragm [36,37] to relax. A later study [29] of the mechanism of this reflex inhibition of the LES found that this response was not blocked by vagotomy, sympathectomy, hexamethonium or atropine, but was blocked by tetrodotoxin. This study determined that this response was neurally mediated, but not mediated by a peripheral or central reflex [29]. Therefore, this effect must have been due to mechanical activation of the inhibitory motor nerve [29]. It was later determined that the motor inhibitory neurons from the esophagus to the LES and crural diaphragm have a mechanoreceptive function [10].

The function of this mechanosensitive inhibitory innervation is elimination of the esophago-gastric barrier, i.e., LES and crural diaphragm contraction. This response is an integral part of both swallowing and belching. During swallowing the peristaltic process activates distal esophageal longitudinal contraction [23,37,42,63] which is closely associated with both LES [23,29,62] and crural diaphragm [36,37,62] relaxation. Similarly, during belching (Figure 7) the gastric air bolus reflexly activates distal esophageal longitudinal contraction before initiation of the belch, and this response is closely associated with relaxation of both the LES and crural diaphragm [29,39,40,49,50]. The actual belch does not occur until the esophago-gastric barrier is reduced enough to allow gastro-esophageal reflux of the air bolus [50,62] which activates the rapidly adapting mucosal receptors [30,50], as described above.

Sympathetic mechanoreceptors

It has been found that distension of the esophagus activates two types of receptors that activate splanchnic nerve afferents [9]. One type is a slowly-adapting muscular tension receptor and the other is a rapidly-adapting touch sensitive serosal receptor.

The function of these receptors is unknown, but since they activate sympathetic afferents, they probably affect the autonomic nervous system. Mechanical stimulation of the esophagus can increase blood pressure [35,41,46] and cause pain [41,64]. Therefore, these esophageal sympathetic activating mechanoreceptors may provide receptive function for these responses. Further studies are needed to identify the mechanoreceptors, and define their responses and functions.

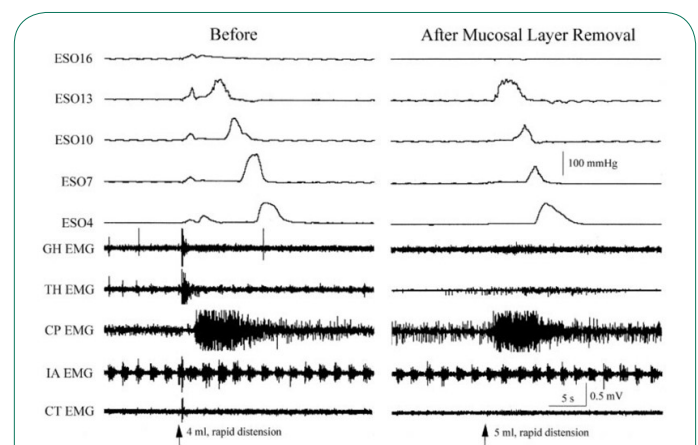


Figure 1: Functions of muscular slowly-adapting and mucosal rapidly-adapting mechanoreceptors. This figure illustrates the effects of removal of the esophageal mucosa on the reflex responses activated by esophageal distension [30]. The arrows indicate the times of injection of air at listed volumes and injection rates. Removal of the mucosal layer blocked the reflexes activated by the rapidly-adapting mucosal mechanoreceptors, i.e., EURR, EGCR, and EHDR; but did not block the reflexes activated by the muscular slowly-adapting mechanoreceptors, i.e., EUCR or SP. The EURR is indicated by the decrease in CP EMG during the stimulus, EGCR by the increase in IA EMG, EHDR by the increase in GH and TH EMG, EUCR by the increase in CP EMG after the stimulus, and SP by the peristaltic wave of manometric pressure after the stimulus. The CP is the primary muscle of the Upper Esophageal Sphincter (UES). This study was conducted in an anesthetized cat. ESO#: Esophagus #; LES: Lower Esophageal Sphincter; EMG: Electromyography; HG: Geniohyoideus; TH: Thyrohyoideus; CP: Cricopharyngeus; IA: Intraaryternoideus; CT: Cricothyroideus.

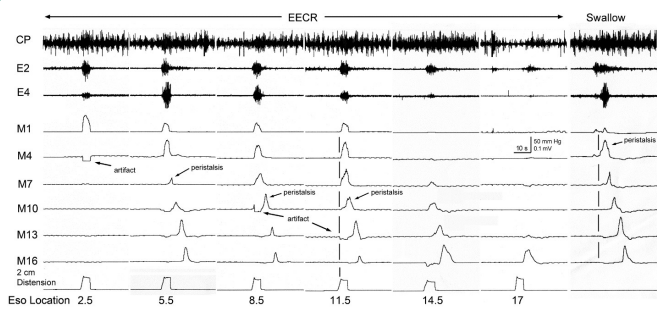


Figure 2: EECR activated by stimulation of the esophageal muscular slowly-adapting tension receptors. This figure depicts the nature of the Esophago-Esophageal Contractile Response (EECR) activated by stimulation of the slowly-adapting muscular tension receptors [35]. Distending the esophagus with a balloon at 2.5 to 17 cm from the UES activated EECR and SP. The simultaneous non-propagating contractions orad of the stimuli are the EECR's and the propagating contractions from the point of stimulation distally are the SP's. When the stimulus was applied at 2.5 cm from the UES, only EECR occurred. Stimuli from 5.5 to 14.5 cm caused of the UES all had both EECR and SP. The comparison of the esophageal responses during primary peristalsis of swallowing with the responses caused by stimulation of the slowly-adapting muscular mechanoreceptors clearly illustrate the non-propagating nature of the EECR. The distending balloon sometimes caused an artifactual rapid reduction in pressure in nearby recording sites. The EECR is more likely to be activated by stimulation of the slowly-adapting muscular tension receptors of the orad esophagus. This study was conducted in the decerebrate cat.

CP: Cricopharyngeus; SP: Secondary Peristalsis; UES: Upper Esophageal Sphincter; E#: EMG Recording # cm from the CP; M#: Manometry Recording # cm from CP; Eso location: Location of the balloon from the CP.

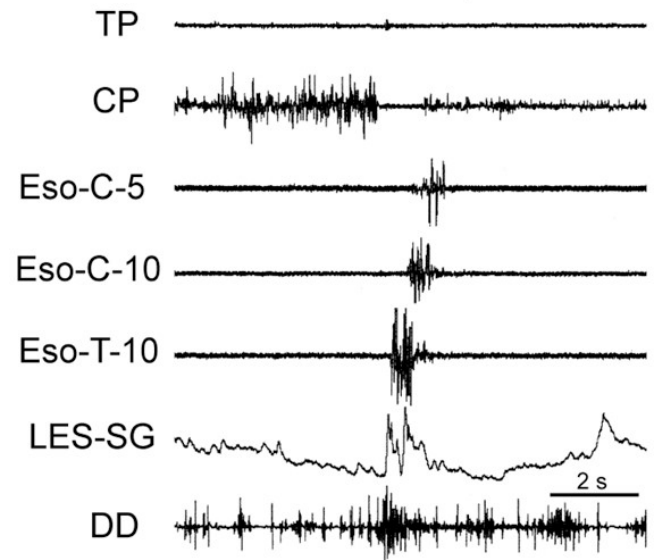


Figure 4: ERPR activated by stimulation of the mucosal rapidly-adapting mechanoreceptors. This figure depicts the Esophageal Retrograde Peristaltic Contraction Response (ERPR) of the esophagus activated by stimulation of the mucosal rapidly-adapting mechanoreceptors during belching [50]. The response begins in the LES at the beginning of the EUCR, lasts the duration of the EUCR, and functions to expel the gastro-esophageal refluxed air bolus from the esophagus. This study was conducted in a chronically instrumented awake dog, and the responses occurred spontaneously.

LES: Lower Esophageal Sphincter; EUCR: Esophago-UES Relaxation Reflex; TP: Thyropharyngeus; CP: Cricopharyngeus; Eso-C-#: Cervical esophagus # cm from the CP; Eso-T-#: Thoracic esophageus #cm from the LES.

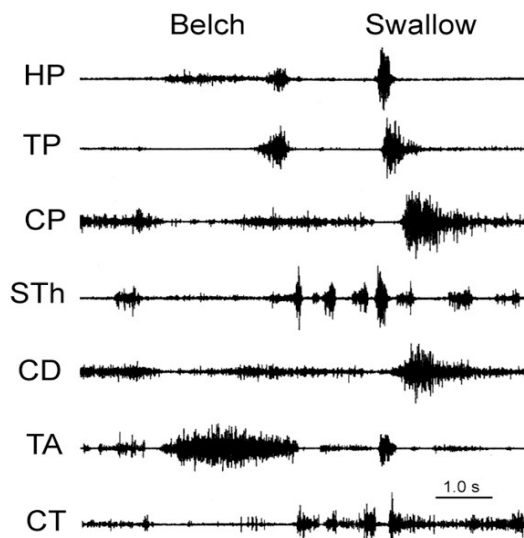


Figure 3: EGCR activated by stimulation of the esophageal mucosal rapidly-adapting touch mechanoreceptors. This figure shows that stimulation of the mucosal rapidly-adapting Esophageal Mechanoreceptors causes Glottal Closure (EGCR) by strong activation of the TA and relaxation of the CD during the period of CP relaxation [50]. The TA acts to close the glottis and the CD acts to open the glottis, therefore, the actions of these muscles would provide significant protection of the airway. This study was conducted in a chronically instrumented awake dog, and the responses occurred spontaneously.

EGCR: Esophago-Glottal Closure Reflex; HP: Hypopharyngeus; TP: Thyropharyngeus; CP: Cricopharyngeus; STh: Stylohyoideus; CD: Cricoarytenoideus Dorsalis; TA: Thyroarytenoideus; CT: Cricothyroideus.

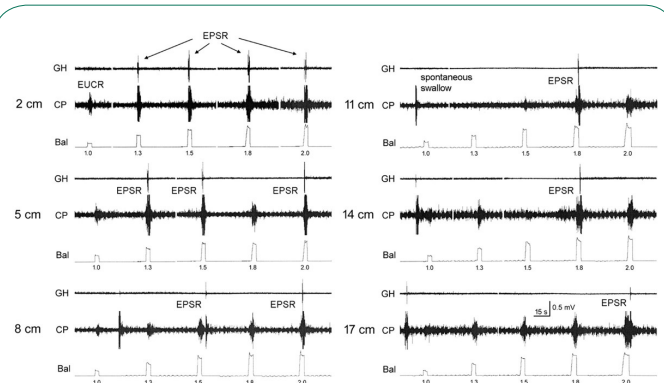


Figure 5: EPSR activated by stimulation of the tension mucosal receptors of the esophagus. This figure depicts the recordings of Geniohyoideus (GH) and Cricopharyngeus (CP) Electromyography (EMG) during esophago-Upper Esophageal Sphincter (UES) Contractile Reflex (EUCR) or esophago-pharyngeal swallow reflex (EPSR) in response to distension of the esophagus at various esophageal locations [33]. The EUCRs are associated with increased CP EMG, and the EPSRs are associated with increased GH and CP-EMG activated in a sequential fashion. Note that only one EPSR was activated per stimulus, and the delays between stimulus and EPSR were variable. EPSRs were more likely to occur at higher distensions and at more rostral esophageal locations of the stimulus. Occasionally, spontaneous swallows occurred between stimuli. Bal, balloon. Balloon distensions were 1.0 -2.0 cm in diameter of a 3-cm-long balloon in the esophagus at 2-17 cm from the CP. This study was conducted in decerebrate cats.

GH: Geniohyoideus; CP: Cricopharyngeus; Bal: Balloon Tension.

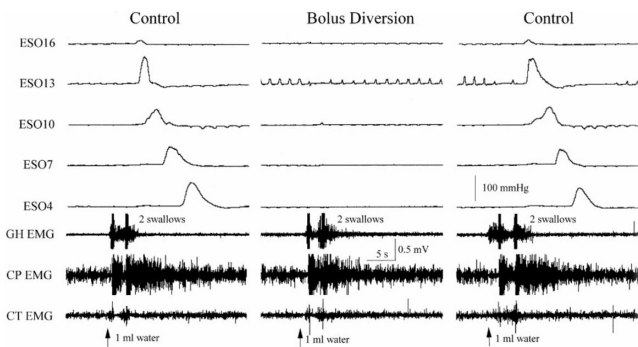


Figure 6: The mucosal slowly adapting tension receptors facilitate the progression from the pharyngeal to esophageal phases of swallowing. This figure shows that diverting a bolus just by turning a stop cock between the pharynx and esophagus eliminates the initiation of the esophageal phase of a 1 ml water bolus stimulated swallow, but this effect also occurs when no bolus is used to initiate the swallow [30]. Therefore, the receptors mediating this function must be very sensitive and applying wall tension to activate these receptors is not necessary. Only mild touching of the esophageal mucosa is necessary and the stimulus need not be rapid. This study was conducted in anesthetized cats.

ESO#: Esophageal Manometry #cm from the LES; GH: Geniohyoideus; CP: Cricopharyngeus; CT: Cricothyroideus; EMG: Electromyography.

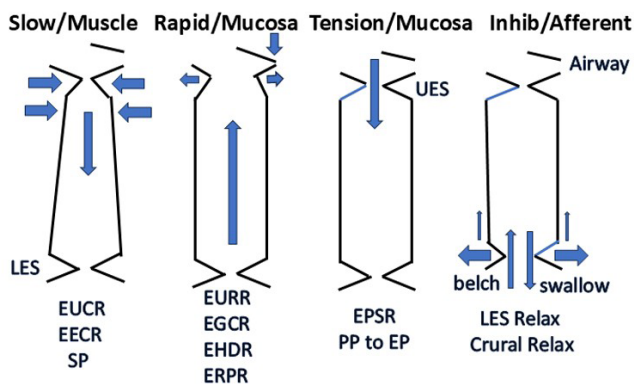


Figure 8: Functions of esophageal mechanoreceptive agents. This figure depicts the functions of each of the four esophageal mechanoreceptive agents, three are mechanoreceptors and one is the mechanoreceptive inhibitory afferent nerve. The slowly-adapting muscular mechanoreceptor (Slow/Muscle) functions to prevent esophago-pharyngeal reflux by activating the EUCR, EECR and SP. The rapidly-adapting mucosal mechanoreceptor (Rapid/Mucosa) functions to mediate belching by activating the EUCR, EGCR, EHDR and ERPR. The slowly adapting mucosal tension receptor (Tension/Mucosa) functions to promote the transition from pharyngeal to esophageal phase of swallowing by activating the pharyngeal phase by Esophageal Stimulation (EPSR). The mechanoreceptive inhibitory afferent innervation of the LES and crural diaphragm (Inhib/Afferent) functions to open the esophago-gastric barrier during swallowing or belching in association with shortening of the distal esophagus.

UES: Upper Esophageal Sphincter; LES: Lower Esophageal Sphincter; EUCR: Esophago-UES Contractile Reflex; EECR: Esophago-Esophageal Contractile Reflex; SP: Secondary Peristalsis; EUCR: Esophago-UES Relaxation Reflex; EGCR: Esophago-Glottal Closure Reflex; EHDR: Esophago-Hyoid Distraction Reflex; ERPR: Esophago-Retrograde Contraction Reflex; EPSR: Esophago-Pharyngeal Swallow Reflex; PP: Pharyngeal Phase; EP: Esophageal Phase.

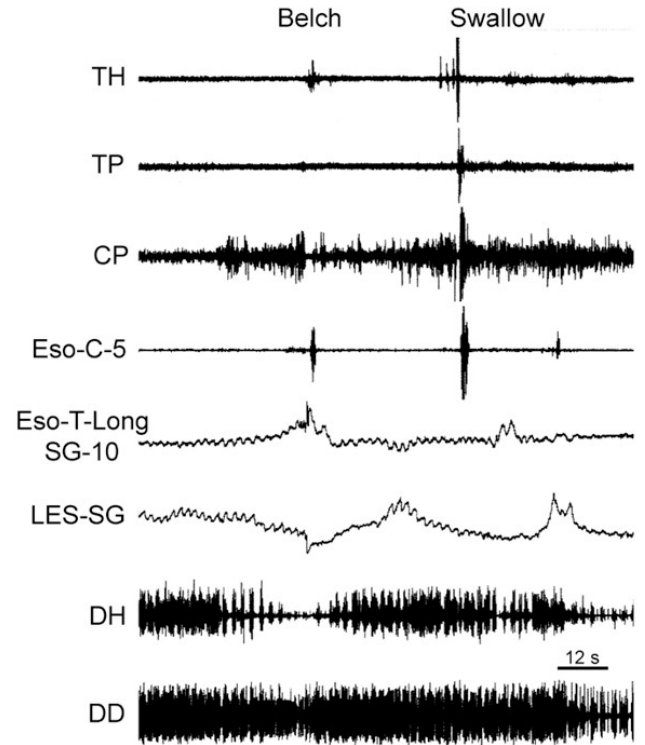


Figure 7: Mechanosensitive esophageal inhibitory innervation response during belching. This figure depicts the responses of the esophagus, diaphragm, and LES associated with eructation and swallowing [50]. Note the simultaneous increase in tone of the longitudinal thoracic esophagus (Eso-T-Long), decrease in tone of the LES (LES-SG), and decrease in respiratory-related phasic activity of the Diaphragmatic Hiatus (DH) during eructation and the comparison with the subsequent swallow. The DH muscle is the crural muscle surrounding the esophagus. This study was conducted in a chronically instrumented awake dog, and the responses occurred spontaneously. The numbers next to abbreviations indicate distance of the recording device from either the CP or LES. If the device is cervical it is cm from CP, if the device is thoracic, its cm from the LES. Also, the diaphragm and thoracic EMG electrodes often have EKG activity superimposed. All recordings are EMG except those designated with SG, which are strain gauge recordings. All SG recordings are in the circular direction unless indicated by the notation, Long, as indicating longitudinally oriented.

TH: Thyrohyoideus; TP: Thyropharyngeus; CP: Cricopharyngeus; Eso: Esophagus; C: Cervical; T: Thoracic; LES: Lower Esophageal Sphincter; DH: Diaphragmatic Hiatus; DD: Diaphragmatic Dome; SG: Strain Gauge.

Conclusions

There are three identified esophageal mechanoreceptors with defined functions. The slowly-adapting muscular mechanoreceptors mediate the following reflex functions which prevent esophago-pharyngeal reflux: EUCR, EECR and SP. The rapidly-adapting mucosal mechanoreceptors mediate belching and its associated reflex responses: EUCR, EGCR, EHDR, and ERPR. The slowly-adapting mucosal tension receptors function to promote bolus transport from pharynx to stomach by activating the EPSR instead of SP, especially in infant humans and animals, and ensuring that the esophageal phase of swallowing follows the pharyngeal phase. In addition, there is the mechanoreceptive inhibitory motor innervation of the LES and crural diaphragm which facilitates emptying of the esophagus during swallowing and gastro-esophageal reflux during belching. Undefined esophageal receptors mediate mechanoreceptive sympathetic afferent activation which probably have nociceptive functions.

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