The role of the superior laryngeal nerve in esophageal reflexes

I. M. Lang, B. K. Medda, S. Jadcherla, and R. Shaker

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Submitted 6 January 2012; accepted in final form 9 March 2012

Lang IM, Medda BK, Jadcherla S, Shaker R. The role of the superior laryngeal nerve in esophageal reflexes. *Am J Physiol Gastrointest Liver Physiol* 302: G1445–G1457, 2012. First published March 8, 2012; doi:10.1152/ajpgi.00007.2012.—The aim of this study was to determine the role of the superior laryngeal nerve (SLN) in the following esophageal reflexes: esophago-upper esophageal sphincter (UES) contractile reflex (EUCR), esophago-lower esophageal sphincter (LES) relaxation reflex (ELIR), secondary peristalsis, pharyngeal swallowing, and belch. Cats (*N* = 43) were decerebrated and instrumented to record EMG of the cricopharyngeus, thyrohyoideus, geniohyoideus, and cricothyroideus; esophageal pressure; and motility of LES. Reflexes were activated by stimulation of the esophagus via slow balloon or rapid air distension at 1 to 16 cm distal to the UES. Slow balloon distension consistently activated EUCR and ELIR from all areas of the esophagus, but the distal esophagus was more sensitive than the proximal esophagus. Transection of SLN or proximal recurrent laryngeal nerves (RLN) blocked EUCR and ELIR generated from the cervical esophagus. Distal RLN transection blocked EUCR from the distal cervical esophagus. Slow distension of all areas of the esophagus except the most proximal few centimeters activated secondary peristalsis, and SLN transection had no effect on secondary peristalsis. Slow distension of all areas of the esophagus inconsistently activated pharyngeal swallows, and SLN transection blocked generation of pharyngeal swallows from all levels of the esophagus. Slow distension of the esophagus inconsistently activated belching, but rapid air distension consistently activated belching from all areas of the esophagus. SLN transection did not block initiation of belch but blocked one aspect of belch, i.e., inhibition of cricopharyngeus EMG. Vagotomy blocked all aspects of belch generated from all areas of esophagus and blocked all responses of all reflexes not blocked by SLN or RLN transection. In conclusion, the SLN mediates all aspects of the pharyngeal swallow, no portion of the secondary peristalsis, and the EUCR and ELIR generated from the proximal esophagus. Considering that SLN is not a motor nerve for any of these reflexes, the role of the SLN in control of these reflexes is sensory in nature only.

pharyngeal swallow; secondary peristalsis; belching; cricopharyngeus; lower esophageal sphincter

THE SUPERIOR LARYNGEAL NERVE (SLN) is a branch of the vagus nerve that provides motor innervation to the cricothyroideus and sensory innervation of the epiglottis, tongue, aryepiglottic fold, and larynx (12). The primary role of these afferents of the SLN is the activation of swallowing (29). However, anatomical (40, 47) and neurophysiological (1, 25, 28) studies have found that the SLN innervates the esophagus, but the role of the SLN afferents in esophageal function is not well understood. Some studies suggest that the SLN afferents from the cervical esophagus mediate pseudoaffective responses to noxious stimulation of the esophagus (13), but no studies have been published to date that have investigated whether this innervation may also serve a physiological function.

There have been many studies of the role of the vagus nerves in various esophageal reflexes (3, 8, 9, 22, 26, 32–34, 36–39, 43), but most of these studies have investigated reflexes from the thoracic esophagus (3, 8, 22, 26, 34, 43) and few have studied reflexes from the proximal cervical esophagus (7, 36). The SLN primarily innervates the proximal cervical esophagus (40, 47) and its role in these reflexes has never been studied.

It was hypothesized (8), and then later shown (9), that the caudally directed fibers of the recurrent laryngeal nerves (RLN), which merge with the vagus nerves, play a role in mediating the esophago-upper esophageal sphincter (UES) contractile reflex (EUCR) from the cervical esophagus, but these studies (9) found that the RLN only mediates this reflex from the distal cervical esophagus and not the proximal cervical esophagus. However, the rostrally directed fibers of the RLN merge with the SLN (1, 28) rather than the vagus nerves, and the role of these fibers in mediating the esophago-UES reflex or any other esophageal reflex has not been investigated.

The extrinsically mediated esophageal reflexes in which the laryngeal nerves could possibly play a role include the EUCR (8, 22), the esophago-lower esophageal sphincter (LES) relaxation reflex [ELIR (3, 34, 36, 43)], secondary peristalsis (22, 26, 43), pharyngeal swallow (7, 16), and belching (22). Therefore, the aim of this study was to determine the role of the SLN in mediating the EUCR, ELIR, secondary peristalsis, pharyngeal swallow, and belching.

**METHODS**

**Animal Preparation**

All studies were conducted under a protocol approved by the Institutional Animal Care and Use Committee of the Medical College of Wisconsin. Cats (*N* = 43) were fasted overnight and decerebrated. The animals were anesthetized with isoflurane (3%), the ventral neck region was exposed, the trachea was intubated, and the carotid arteries were ligated. The skull was exposed and a hole over a parietal lobe was made by use of a trephine. The hole was enlarged by use of rongeurs, the central sinus was ligated and cut, and the brain was severed midcollicularly with a metal spatula. The forehead was then suctioned out of the skull and the blood vessels of the circle of Willis were coagulated by suction through cotton balls soaked in warm saline. The bony sinuses were filled with bone wax, and the exposed brain was covered with paraffin oil-soaked cotton balls, and the skull over the skull was sewn closed. The animals were then placed supine on a heating pad (Harvard Homeothermic monitor) and the body temperature was maintained between 38 and 40°C.

For studies involving the pharynx and larynx (*N* = 25), i.e., EUCR, belching and pharyngeal swallowing, bipolar EMG electrodes were placed into the cricopharyngeus (CP), geniohyoideus, thyrohyoideus, and cricothyroideus. The skin of the neck was then sewn closed.

For studies of the lower esophageal sphincter (*N* = 18), i.e., ELIR, the chest was opened at the xyphoid process through the diaphragm.
No significant differences in mean values were observed. *,†
P
tukey’s were used for all sites, but 1 cm from UES. Student’s esophageal sphincter. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of reflexes. ANOVA and of animals in which the reflex was tested. EUCR, esophago-UES contractile reflex; ELIR, esophago-LES relaxation reflex; SP, secondary peristalsis; UES, upper esophageal sphincter (UES) EMG activity. Note the increased sensitivity of the distal esophagus to both reflexes and the relationship of the magnitude of responses to a spontaneous swallow. CP, cricopharyngeus; Bal, distending balloon pressure. Vertical axis is distance of the stimulating balloon from the UES, and horizontal axis is the distending diameter.

and the animals were placed on a ventilator with the tidal volume set at 15 ml/kg body wt at 20 breaths/min and positive end-expiratory pressure of 3–5 cm of water. The phrenic nerves were cut, and the diaphragm was transected and removed from the esophagus. A strain gauge was sewn onto the LES under tension to allow recording of pressures. Vertical axis is distance of the stimulating balloon from the UES, and horizontal axis is the distending diameter.

In all animals the femoral vein was cannulated for infusion of saline, the femoral artery was cannulated to record arterial blood pressure, and a gastric fistula was formed to allow drainage of gastric secretions. A two-site (3 cm apart) solid-state pressure transducer (Gaeltec) was placed into the esophagus through the mouth and used to record intraluminal pressures of the esophagus. A catheter was placed into the esophagus through the mouth and used to distend the esophagus slowly or rapidly at various locations.

After obtaining control responses to esophageal distension, the effects of transection of SLN, RLN, or vagus nerves were investigated. The SLN were located between the nodose ganglia and the insertion of the SLN into the pharyngeal musculature, the RLN were located on either side of the trachea in the lower cervical area or just caudal to their insertion into the larynx, and the vagus nerves were identified in the neck at the level of the larynx.

Recording of Responses

DC recordings. The femoral arterial catheter as well as the esophageal distending catheter were attached to Statham pressure transducers, and the strain gauge was attached to a bridge circuit. The output signals from these devices as well as the output from the esophageal solid-state pressure transducers were attached to Grass P122 low-level DC amplifiers set at 3 Hz high-frequency cutoff filtration.

EMG recordings. The EMG electrodes were attached to A-M Systems differential AC amplifiers set at 1,000 gain, 10 Hz to 1 kHz band-pass filtration, and 60-Hz notch filtration.

Computer data acquisition. All data were acquired and analyzed by use of Dataq Instruments data-acquisition hardware and software.

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
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<th>13</th>
<th>16</th>
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<tbody>
<tr>
<td>EUCR</td>
<td>1.3 ± 0.1 (32/32)</td>
<td>1.3 ± 0.1 (32/32)</td>
<td>1.3 ± 0.1 (32/32)</td>
<td>1.2 ± 0.1 (32/32)</td>
<td>1.2 ± 0.1 (32/32)</td>
<td>1.2 ± 0.1 (32/32)</td>
</tr>
<tr>
<td>ELIR</td>
<td>1.6 ± 0.1* (18/18)</td>
<td>1.6 ± 0.1* (18/18)</td>
<td>1.6 ± 0.1* (18/18)</td>
<td>1.4 ± 0.1 (18/18)</td>
<td>1.2 ± 0.1 (18/18)</td>
<td>1.3 ± 0.1 (18/18)</td>
</tr>
<tr>
<td>SP</td>
<td>1.8 (1/25)†</td>
<td>1.6 ± 0.1* (8/25)†</td>
<td>1.5 ± 0.1* (22/25)</td>
<td>1.5 ± 0.1* (23/25)</td>
<td>1.4 ± 0.1 (23/25)</td>
<td>1.3 ± 0.1 (23/25)</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. EUCR, esophago-UES contractile reflex; ELIR, esophago-LES relaxation reflex; SP, secondary peristalsis; UES, upper esophageal sphincter. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of reflexes. ANOVA and Tukey’s were used for all sites, but 1 cm from UES. Student’s t-test was used for 1 cm from UES. Fisher’s exact test was used for all contingency table analyses. No significant differences in mean values were observed. * 0.05 for a difference between EUCR and ELIR at each level of the esophagus.
Stimulation of the Esophagus

For stimulation of reflexes activated by slow distension of the esophagus, i.e., EUCR, ELIR, secondary peristalsis, and pharyngeal swallow, the esophagus was distended by the inflation of a balloon at the end of the catheter inserted into the esophagus. The balloon was 1.5 cm long and distended by hand for 5 s with a syringe. The distensions were 1 ml (1 cm diameter), 2 ml (1.3 cm diameter), 3 ml (1.6 cm diameter), 4 ml (1.8 cm diameter), 5 ml (2.0 cm diameter), or 7.5 ml (2.3 cm diameter).

For reflexes activated by rapid distension of the esophagus, i.e., belching, the esophagus was distended by a pulse of air directed laterally from a small hole in the side of a plastic catheter attached to a pneumatic PicoPump (World Precision Instruments). The pulse of air was applied at 8–12 psi for 50 ms.

In both situations the distending catheter was attached to a pressure transducer as described above and the signal was used as a stimulus marker.

Experimental Protocols

Effects of esophageal distension. The esophagus was distended slowly or rapidly from 1 to 16 cm below the UES in 3-cm increments at six locations. The first three sites, 1, 4 and 7 cm from the CP, were within the cervical region, and the last three sites, 10, 13, and 16 cm, were within the thorax. The length of the esophagus of the cat is 16–18 cm.

Effects of nerve transection. After obtaining control responses to distension, we severed the SLN, RLN, or vagus nerves and repeated the control stimuli. The SLN were cut as they traversed from their insertion in the pharynx and attachment to the nodose ganglia. The RLN were cut just caudal to the larynx or as distally in the cervical area as possible. The vagus nerves were cut in the neck. A second nerve was often cut if all of the responses to esophageal distension were not blocked by the first transection.

Data Reduction and Analysis

Responses from the EMG electrodes and the strain gauge were recorded and the distension volumes required to initiate responses were recorded as threshold volumes, but the magnitudes of these responses were not quantified. Comparison of the magnitudes of EMG (11) and strain-gauge relaxation responses (24) among animals is difficult, because the magnitudes of responses with use of these techniques depend highly on the manner in which the electrodes or strain gauges are sewn onto the muscles. However, the goal of these studies was to identify the role of various afferent neural pathways in mediating reflexes and not to compare the magnitude of responses to esophageal stimulation.

The reflex responses were quantified as the minimum threshold volumes or distension diameters required to activate the reflexes. The mean threshold volumes of the experimental group were compared with the control group by the paired Student’s t-test when there were two groups to compare and ANOVA with Tukey’s post hoc test when there were more than two groups to compare. Differences in the contingency analysis of the success of initiation of reflexes were determined by the Fisher’s exact test. A P value of 0.05 or less was considered significant for all tests.

Fig. 4. Effects of slow distension of the esophagus on activating the belch response and comparison with the EUCR generated from the same location and spontaneous pharyngeal swallowing. Note that slow distension of the same area of the esophagus can activate either the belch or the EUCR. ESO, esophageal pressure.
RESULTS

Control Responses

EUCR: esophago-UES contractile reflex. We found that slow distension of all portions of the esophagus activated (Fig. 1, Table 1) the EUCR in all animals tested. In 5 of 32 animals, the site at 16 cm from the UES was outside of the esophagus. The threshold sensitivity of the EUCR did not significantly differ between the cervical and thoracic portions of the esophagus whether the animals had a thoracotomy or not (Fig. 2). Therefore, we pooled all of the EUCR data and found that there was no significant ($R^2 = 0.60, P > 0.05$) linear relationship between threshold sensitivity and location of the stimulus in the esophagus.

ELIR: esophago-LES relaxation reflex. We found that slow distension of all portions of the esophagus activated (Fig. 1, Table 1) the esophago-LES inhibitory reflex (ELIR) in all animals tested. In 3 of 18 animals the site at 16 cm from the UES was outside of the esophagus. There was a significant ($R^2 = 0.79, P < 0.02$) linear relationship between threshold sensitivity and location of the stimulus in the esophagus. The ELIR was more sensitive distally than proximally in the esophagus (Fig. 2).

Secondary peristalsis. We found that slow distension of the esophagus activated secondary peristalsis starting somewhere in the esophagus in every animal, $n = 25$, in which secondary peristalsis could be accurately determined (Table 1). The site 1 cm from the UES was almost insensitive to this reflex response as secondary peristalsis was only activated in 1 of 25 animals (Table 1). Excluding the response at 1 cm from the UES we found that there was a significant linear relationship ($R^2 = 0.96, P < 0.01$) between threshold sensitivity for activation of secondary peristalsis and location of the stimulus in the esophagus. Similar to the ELIR, activation of secondary peristalsis was most sensitive in the distal rather than the proximal esophagus.

Pharyngeal swallowing. Unlike the EUCR, ELIR, and secondary peristalsis, we could not elicit the pharyngeal swallow by slow distension of the esophagus in every animal. Pharyngeal swallowing was successfully activated in 11 of 19 animals that were instrumented to allow recording of the pharyngeal swallow (Fig. 3). However, the pharyngeal swallow was not successfully activated at each esophageal site in each of these 11 animals. There was a significant ($r^2 = 0.81, P < 0.02$) linear relationship between sensitivity of activation of the pharyngeal swallowing and location of the stimulus in the esophagus.

Belching. We observed a belch response to slow distension of the esophagus in 6 of the 19 animals that were instrumented to allow recording of the belch response (Fig. 4, Table 2). These belch responses to slow esophageal distension were observed at only some levels of the esophagus in the respond-

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Table 2. Sensitivity of various esophageal reflexes at different levels of the esophagus: reflexes with inconsistent effects

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>1.4 ± 0.1 (8/19)</td>
<td>1.5 ± 0.1 (5/19)</td>
<td>1.7 ± 0.1 (7/19)</td>
<td>1.6 ± 0.1 (7/19)</td>
<td>1.7 ± 0.1 (3/19)</td>
<td>1.7 ± 0.1 (2/19)</td>
</tr>
<tr>
<td>Belch</td>
<td>2.0 (1/19)</td>
<td>1.8 (1/19)</td>
<td>2.0 ± 0.2 (3/19)</td>
<td>1.7 ± 0.3 (2/19)</td>
<td>1.7 ± 0.2 (5/19)</td>
<td>1.6 (1/19)</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. PS, pharyngeal swallow. Note that not all animals in which a reflex response could be attained at some level of the esophagus were able to excite the reflex at all levels of the esophagus.
ing animals, and the points of activation differed among animals (Table 2).

Rapid esophageal distension using 8–12 psi at 50 ms activated the belch response in all of the animals tested, \( n = 6 \), and at all levels of the esophagus (Figs. 5, 6, and 7). We did not statistically examine differences in threshold sensitivities of belch response at different levels of the esophagus.

Comparison of Control Responses to Esophageal Distension

The responses to slow distension of the esophagus occurred in two sets: those that were activated in a very consistent manner such that the response occurred in every animal examined and at virtually every esophageal site within each animal, and those in which the responses to distension were very inconsistent such that the response was not observed in every animal and at every esophageal site in the responsive animals. The consistent responses to slow distension included the EUCR, ELIR, and secondary peristalsis (Table 1), and those that were inconsistent included pharyngeal swallow and belching (Table 2).

We compared the threshold sensitivities of the three consistent responses to slow esophageal distension and found that the EUCR was more sensitive than the ELIR at 1–7 cm from the UES and more sensitive than the secondary peristalsis at 4–10 cm from the UES (Table 1). No differences in threshold sensitivities were found for these three reflexes at the most
distal two sites in the esophagus. Secondary peristalsis was activated at every level of the esophagus at sensitivities similar to those for activation of the ELIR, except at the site closest to the UES (Table 1). The success of activation of secondary peristalsis was less than that of activation of the EUCR or ELIR at 1, 4, and 16 cm from the UES (Table 1).

Although in most sites the EUCR, ELIR, and secondary peristalsis were successfully activated at a minimum of 84%, the pharyngeal swallow was successfully activated at most at a rate of 42% (Tables 1 and 2). Unlike the ELIR and secondary peristalsis, the sensitivity of pharyngeal swallow was greater at the proximal than the distal portion of the esophagus. Although there were too few belch responses to statistically compare threshold sensitivities with EUCR, ELIR, secondary peristalsis, or pharyngeal swallow activated by slow esophageal distension, the observed single or mean values of threshold sensitivity of the belch response were greater at all levels of the esophagus, except the most distal, than the mean values for activation the other reflexes (Tables 1 and 2).

Effects of Nerve Transection

EUCR. Transection of the SLN either blocked the successful activation of EUCR or reduced the sensitivity of activation of the EUCR generated from the cervical, but not thoracic, esophagus (Fig. 8, Table 3). Subsequent vagotomy blocked the successful activation of the EUCR from the entire esophagus (Fig. 8, Table 3). Vagotomy blocked or significantly reduced the successful activation of the EUCR from the distal 12 cm of the esophagus that included all of the thoracic portion and the distal end of the cervical portion of the esophagus (Fig. 9, Table 4). Subsequent transection of the RLN just distal to the larynx blocked the successful activation of the EUCR from the remainder of the esophagus (Fig. 9, Table 4).

Transection of the RLN just distal to the larynx blocked the successful activation of the EUCR or reduced the sensitivity of activation of the EUCR from the cervical esophagus only (Fig. 10, Table 5). Subsequent transection of the vagus nerves blocked the successful activation of the EUCR from the remainder of the esophagus (Table 5). Transection of the RLN in the distal cervical region blocked (Fig. 11) or significantly reduced (Table 6) the threshold sensitivity of the EUCR generated from the distal cervical region only.

ELIR. Transection of the SLN blocked the successful activation or significantly reduced the sensitivity of activation of the ELIR generated from the cervical, but not thoracic esophagus (Fig. 8, Table 7). Vagotomy after SLN transection blocked the successful activation of the ELIR from the cervical esophagus and significantly reduced the sensitivity of activation of the ELIR generated from the thoracic esophagus only (Fig. 8, Table 7).

We found that vagotomy blocked the successful activation of the ELIR from the cervical portion of the esophagus and significantly reduced the sensitivity of activation of the ELIR generated from the thoracic portion of the esophagus (Fig. 9, Table 8).

Secondary peristalsis. We found that transection of the SLN had no effect on the successful activation of secondary peristalsis or the threshold sensitivity for activation of secondary peristalsis generated by slow esophageal distension (Table 9).

Pharyngeal swallowing. We found that transection of the SLN or RLN just distal to the larynx, but not vagotomy, blocked successful activation of pharyngeal swallow generated

### Table 3. Effect of SLN transection followed by vagotomy on EUCR

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.3 ± 0.1 (8/8)</td>
<td>1.2 ± 0.1 (8/8)</td>
<td>1.3 ± 0.1 (8/8)</td>
<td>1.3 ± 0.1 (8/8)</td>
<td>1.2 ± 0.1 (8/8)</td>
<td>1.2 ± 0.1 (8/8)</td>
</tr>
<tr>
<td>SLN section</td>
<td>NR (0/8)</td>
<td>2.0 (1/8)†</td>
<td>1.7 ± 0.1* (8/8)</td>
<td>1.6 ± 0.1 (8/8)</td>
<td>1.2 ± 0.1 (8/8)</td>
<td>1.4 ± 0.1 (8/8)</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>NR (0/4)†</td>
<td>NR (0/4)†</td>
<td>NR (0/4)†</td>
<td>NR (0/4)†</td>
<td>NR (0/4)†</td>
<td>NR (0/4)†</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. SLN, superior laryngeal nerve; NR, no response. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of reflexes. Student’s *t*-test was used to test the effects of SLN transection on sensitivities of EUCR at the same esophageal sites, except for the sites at 1 and 4 cm from the esophagus. Fisher’s exact test was used for all contingency table analyses. *: *t* < 0.05 for a difference from control.

Fig. 8. Effect of SLN transection and subsequent vagotomy on the EUCR and ELIR. Note that SLN transection blocked or inhibited both the EUCR and ELIR activated from the proximal esophagus. Subsequent vagotomy blocked the EUCR from the entire esophagus and blocked or inhibited the ELIR from the remainder of the esophagus. Also note the magnitude of responses relative to a spontaneous swallow. All distensions were at 2 cm. EB, esophageal balloon marker pressure.
by slow esophageal distension from both the cervical and thoracic portions of the esophagus (Fig. 12, Table 10). Vagotomy also had no effect on the threshold sensitivity for activation of pharyngeal swallow at all levels of the esophagus.

Belching. There were too few belches activated and the belches were too inconsistently activated when slow distension was used to investigate the role of the SLN in this response; however, rapid distension consistently activated the belch response. We found that SLN transection blocked, in three of three animals, inhibition of CP EMG during the belch and had only a small effect on the EMG responses of the TH and CT and subsequent vagotomy blocked all responses (Fig. 5). On the other hand, in three of three animals vagotomy blocked the entire belch response (Fig. 6). After vagotomy, rapid esophageal distension activated either EUCR (Fig. 6) or the pharyngeal swallow (Fig. 7). Subsequent SLN transection blocked the EUCR and pharyngeal swallowing (Fig. 6 and 7).

**DISCUSSION**

We found that slow distension of the esophagus activated the EUCR, ELIR, secondary peristalsis, pharyngeal swallow, and belching; however, the sensitivities and consistencies of the activation of these reflexes indicated that they occurred in two separate sets. The EUCR, ELIR, and secondary peristalsis responded to the applied stimulus in every animal attempted, and at every activated esophageal site the response rate was very high. On the other hand, pharyngeal swallow and belching occurred quite inconsistently and unpredictably since they did not occur in every animal or at every esophageal site in responsive animals. Therefore, it is likely that the EUCR, ELIR, and secondary peristalsis were activated by a common receptor different from those activating pharyngeal swallow and belch.

Prior studies have shown that EUCR and secondary peristalsis are mediated by mechanoreceptors of the esophageal muscularis (22) that respond to slow distension, and the only mechanoreceptor identified in the esophageal muscularis is the intraganglionic laminar ending (41), which is a slowly adapting mechanoreceptor (45, 48). Therefore, it is likely that the ELIR as well as the EUCR and secondary peristalsis are mediated by the slowly adapting mechanoreceptors of the esophageal muscularis.

Rapid distension of the esophagus consistently activated belching confirming our prior studies that found that belching

**Table 4. Effects of vagotomy followed by RLN transaction on EUCR**

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
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<th>7</th>
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<tr>
<td>Control</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
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<td></td>
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<td>(7/7)</td>
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<tr>
<td>Vagotomy</td>
<td>1.4 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>(6/6)</td>
<td>(2/6)†</td>
<td>(0/6)†</td>
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<td>(0/4)†</td>
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</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. RLN, recurrent laryngeal nerve. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of reflexes. Student’s t-test was used to test the effects of vagotomy on sensitivities of EUCR at the same esophageal sites, except for the sites at 1 and 4 cm from the esophagus. Fisher’s exact test was used for all contingency table analyses. †P < 0.05 for a difference from control.
is mediated by rapidly adapting mechanoreceptors of the esophageal mucosa (22).

The pharyngeal swallow is probably not mediated by the muscular mechanoreceptors, as described above, but it also is probably not mediated by mucosal receptors responsive to rapid mechanical stimuli. Although rapid esophageal distension was capable of activating the pharyngeal swallow, the pharyngeal swallow occurred inconsistently as it did with slow distension. Therefore, it is unclear which receptor mediates activation of the pharyngeal swallow; however, slowly adapting mechanoreceptors have been found in the esophageal mucosa (25) and these receptors might mediate this reflex response.

We found in the cat that the sensitivity of activation of the EUCR tended to be greater in the thoracic than cervical esophagus, but the difference was not statistically significant. However, others found in the cat that activation of the EUCR was significantly more sensitive in the thoracic than cervical esophagus (8). On the other hand, the magnitude of the UES response during the EUCR in humans (2, 4) and in cats (8, 35) was greater when activation was more rostral (2, 4). We did not quantify differences in magnitudes of responses because it is difficult to compare the absolute magnitudes of EMG and strain gauge activities among animals since the magnitude of the responses from these devices depends greatly on how they are sewn onto the muscle (11, 24).

Contrary to the EUCR, the sensitivity of the ELIR was significantly greater in the thoracic than cervical portions of the esophagus. This observation supports prior findings in the dog (4) as well as in the human (2).

Of all of the reflexes activated by slow distension we found the EUCR to be the most sensitive, especially in the cervical region. No other published study examined all of these reflexes simultaneously in the same animals; therefore, it is difficult to compare this result to that of other studies. However, one laboratory studied both the EUCR and ELIR in two separate experimental studies in dogs (8, 35), and they also found that the esophagus is more sensitive to stimulation of the EUCR than the ELIR. The physiological significance of this finding is unknown, but perhaps this priority is related to the primacy of airway protection, served by the EUCR, over bolus transport, served by ELIR or the other reflexes. That is, it is more important to prevent the bolus from being refluxed into the pharynx and possibly aspirated than it is for the bolus to be moved from the esophagus to the stomach.

There have been numerous studies of secondary peristalsis (32), but we could find only one study (7) in which this reflex was tested very close, i.e., within 2 cm, to the UES. This study in humans (7) found that the most proximal portion of the esophagus is insensitive to activation of secondary peristalsis by balloon distension. We confirmed this finding in the cat. Enzmann et al. (7) suggested that this lack of the ability to stimulate secondary peristalsis in the cervical esophagus may be related to differences between innervations of smooth and striated muscles, because in humans only those areas of the esophagus.

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.0</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vagal section</td>
<td>(6/6)†</td>
<td>(6/6)†</td>
<td>(6/6)†</td>
<td>(6/6)†</td>
<td>(6/6)†</td>
<td>(6/6)†</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of reflexes. Student’s t-test was used to test the effects of vagotomy on sensitivities of EUCR at the same esophageal sites, except for the sites at 1 and 4 cm from the esophagus. Fisher’s exact test was used for all contingency table analyses. *, †P < 0.05 for a difference from control.
esophagus from which secondary peristalsis could not be elicited had striated muscle esophagus. This hypothesis is unlikely because in the cat striated muscle extends well into the thoracic esophagus, which is sensitive to the activation of secondary peristalsis. Therefore, differences in control of secondary peristalsis are not related to differences in the innervation of the different types of esophageal muscles but are most likely related to differences in innervation patterns of different esophageal functions.

We hypothesize that the inability to activate secondary peristalsis from the proximal cervical esophagus serves an airway protective function. Considering that within the striated muscle portion of the esophagus secondary peristalsis usually begins proximal to the region distended (7, 33), a stimulus applied close to the UES has no opportunity to begin at an oral location. If the secondary peristalsis did begin at this site, it might cause esophagopharyngeal reflux and aspiration. The lack of secondary peristalsis just below the UES does not mean there is no mechanism to remove material at this position because another relevant reflex is present as described below.

Distension, slow or rapid, of the esophagus can activate a pharyngeal swallow, but the most appropriate stimulus to activate this reflex is unknown. Pharyngeal swallows can be activated by mechanical or chemical stimulation of the esophagus in human infants (16), but no applied stimulus was capable of activating this response consistently. Although esophageal distension-induced pharyngeal swallowing is a common finding in the cat and the human infant, it has been reported to occur in only one adult human one time (7). The paucity of data regarding this reflex in adult humans may be partly due to the lack of studies that have investigated this portion of the esophagus in adult humans. Therefore, esophageal stimulation can activate the pharyngeal swallow in humans and animals, but the most appropriate stimulus is unknown. However, it is likely that this reflex is most important when the activating stimulus is in the most proximal portion of the esophagus.

We found in cats and others have found in human infants (16) that the proximal esophagus is most sensitive to stimulation of pharyngeal swallows. The increased sensitivity of the proximal esophagus to the pharyngeal swallow may compensate for the decreased sensitivity of this region to activation of secondary peristalsis, as described above. The rarity of this reflex in adult humans, but commonness in human infants and cats, suggests that there might be a relationship between the presence of this reflex and some commonality between animals and human infants that is not evident with adult humans. One such commonality is the position of the larynx in the neck. Those organisms, i.e., animals and human infants, that have a non-descended larynx are sensitive to this reflex and those, i.e., adult humans, that have a descended larynx are not. Therefore, perhaps, the organisms with a non-descended larynx are more prone to esophagopharyngeal reflux and, therefore, require an esophagopharyngeal swallow reflex for airway protection. However, more studies are needed to resolve this issue.

We found that rapid esophageal distension activated the belch response, which confirmed our prior report that belching is mediated by rapidly adapting esophageal mechanoreceptors (22). On the other hand, slow balloon distension of the esophagus occasionally and unpredictably also activated belching. Since the only identified mechanoreceptor of the muscularis is the slowly adapting mechanoreceptor, and slow distension activated belching very poorly, it is likely that this rapidly adapting mechanoreceptor is located in the mucosa, as we demonstrated previously (22). Electrophysiological studies have found that rapidly adapting esophageal mucosal mechanoreceptors are preferentially activated by stroking with fine hairs (30, 31), but they can also be activated by balloon distension although less successfully (44). Therefore, it is likely that the rubbing of the balloon on the surface of the

### Table 6. Effects of distal RLN transection on EUCR

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.6</td>
<td>1.3</td>
<td>1.5</td>
<td>1.7</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Distal RLN section</td>
<td>1.5</td>
<td>1.6</td>
<td>2.4</td>
<td>1.8</td>
<td>1.5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of reflexes. Student’s t-test was used to test the effects of vagotomy on sensitivities of EUCR at the same esophageal sites. Fisher’s exact test was used for all contingency table analyses. *P < 0.05 for a difference from control.

### Table 7. Effects of SLN transaction followed by vagotomy on ELIR

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.4</td>
<td>1.6</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>(7/7)</td>
<td>(7/7)</td>
<td>(7/7)</td>
<td>(7/7)</td>
<td>(7/7)</td>
<td>(6/7)</td>
</tr>
<tr>
<td>SLN section</td>
<td>2.0</td>
<td>2.0</td>
<td>1.7</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>(1/7)†</td>
<td>(2/7)†</td>
<td>(6/7)</td>
<td>(7/7)</td>
<td>(7/7)</td>
<td>(6/7)†</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1.9</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>(0/4)†</td>
<td>(0/4)†</td>
<td>(0/4)†</td>
<td>(3/4)</td>
<td>(4/4)</td>
<td>(4/4)</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of ELIR. Student’s t-test was used to test the effects of SLN transection on sensitivities of ELIR at the same esophageal sites, at 1, 4, and 7 cm from the UES, and ANOVA with Tukey’s was used for sites 10, 13 and 16 cm from the UES except for the sites at 1 and 4 cm from the esophagus. Fisher’s exact test was used for all contingency table analyses. †P < 0.05 for a difference from control.
mucosa occasionally activated the mucosal rapidly adapting receptors to cause belching. Therefore, there is no scientific evidence to suggest that the esophageal reflexes differ because of differences in muscle composition of the esophagus.

The RLN supplies motor innervation to the larynx (5), but its role in mediating esophageal reflexes is unclear. After vagal anesthesia in dogs failed to block the EUCR generated from the proximal esophagus, Freiman et al. (8) hypothesized that the EUCR from the proximal esophagus was mediated by afferents in the caudally directed fibers of the RLN, which in turn connected to the vagus nerves. This theory was partially confirmed when Fukunaga et al. (9) found in dogs that cutting the caudally directed fibers of the RLN blocked the EUCR from a position in the cervical esophagus 10 cm from the UES, but not 5 cm from the UES. We found that the rostrally directed fibers of the RLN, which connect with the SLN, mediated the afferent neural pathway of the EUCR generated from the proximal cervical esophagus.

Neurophysiological (28) and anatomical (40, 47) studies have found that afferents from the cervical esophagus project to the nodose ganglion through the SLN. Our studies are the first to provide direct evidence that fibers from the proximal esophagus projecting cranially through the SLN mediate the EUCR from the cervical esophagus, and the first studies to determine a functional role for the SLN afferents from the esophagus (Fig. 13). Our findings also corroborate Fukunaga et al.’s (9) findings and Freiman et al.’s (8) speculations that the EUCR generated from the distal cervical esophagus, 10 cm in the dog and 7 cm in the cat, is mediated by caudally projecting fibers of the RLN through the vagus nerves. We found that vagotomy blocked the ELIR generated from the cervical esophagus only, but also inhibited the ELIR generated from the thoracic esophagus. Considering that the vagus nerves are the efferent pathway for the ELIR from the thoracic esophagus (3), this result confirms that a peripheral pathway inhibitory to the LES exists in most of the thoracic esophagus (17, 27, 34). Others (34) have suggested that vagal efferents provide facilitation of this peripherally mediated LES

Table 8. Effects of vagotomy on ELIR

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.9 ± 0.3 (8/8)</td>
<td>1.9 ± 0.2 (8/8)</td>
<td>1.7 ± 0.2 (8/8)</td>
<td>1.4 ± 0.2 (8/8)</td>
<td>1.1 ± 0.2 (8/8)</td>
<td>1.1 ± 0.2 (8/8)</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>NR (0/8)†</td>
<td>NR (0/8)†</td>
<td>NR (0/8)†</td>
<td>1.8 ± 0.3* (4/8)</td>
<td>1.6 ± 0.3* (6/8)</td>
<td>1.4 ± 0.4* (8/8)</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. ELIR, esophago-LES contractile reflex; LES, lower esophageal sphincter; NR, no response. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of ELIR. Student’s t-test was used to test the effects of vagotomy on sensitivities of ELIR at the same esophageal sites, except for the sites at 1, 4, and 7 cm from the esophagus. Fisher’s exact test was used for all contingency table analyses. †P < 0.05 for a difference from control.

Table 9. Effect of SLN transection on secondary peristalsis (SP)

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.8 (1/25)</td>
<td>1.6 ± 0.1 (8/25)</td>
<td>1.5 ± 0.1 (22/25)</td>
<td>1.5 ± 0.1 (23/25)</td>
<td>1.4 ± 0.1 (21/25)</td>
<td>1.3 ± 0.1 (10/25)</td>
</tr>
<tr>
<td>SLN section</td>
<td>NR (0/10)</td>
<td>1.8 ± 0.2 (3/10)</td>
<td>1.6 ± 0.1 (9/10)</td>
<td>1.6 ± 0.1 (10/10)</td>
<td>1.5 ± 0.2 (9/10)</td>
<td>1.7 ± 0.1 (2/10)</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of secondary peristalsis. Student’s t-test was used to test the effects of SLN transection on sensitivities of secondary peristalsis at the same esophageal sites, except at 1 cm from the UES. Fisher’s exact test was used for all contingency table analyses. No significant differences were found.
inhibitory reflex, but our results suggest that the vagal efferents do not just mediate central facilitation, they mediate the efferent fibers of an extrinsically mediated reflex from the thoracic esophagus. That is, transection of the SLN, which does not carry efferent fibers inhibitory to the LES, reduced the response of the ELIR from the proximal portion of the thoracic esophagus. Our prior c-Fos studies (23) in cats support this conclusion, as we found that slow distension of the thoracic esophagus activated neurons in the caudal dorsal motor nucleus (DMNc), which others (42) have shown to be a motor nucleus for inhibition of the LES. Thus the reflex arc of the ELIR consists of slowly adapting muscular mechanoreceptors of the esophagus, afferents in the SLN, central processing in the DMNc, and efferents in the vagus nerves (Fig. 13).

As discussed above, pharyngeal swallowing and secondary peristalsis activated by distension of the esophagus are complementary in nature. That is, one begins in function where the other one ends. This nature is also reflected in the innervation since we found that the pharyngeal swallow is mediated by the SLN but not the vagus nerves, and secondary peristalsis is not mediated by the SLN, but others (39) have found that it is mediated by the vagus nerves (Fig. 13).

The neural control of the belch response is unlike that of the other reflexes. Whereas in the other reflexes one nerve mediates the entire event from any location, the full belch response generated at any level of the esophagus depends on two nerves. Although vagotomy blocked initiation of the belch response, SLN transection blocked one aspect of the belch, i.e., the inhibition of the CP (Fig. 13). Considering that the only motor nerve of the CP is the pharyngoesophageal nerve in the cat (14), the effect of SLN transection is not likely to have been due to a peripheral effect. In addition, since SLN afferents mediate the increase in CP EMG during the EUCR generated from the proximal esophagus, it is unlikely that SLN afferent activation during the belch response caused relaxation of the CP by inhibition of CP motor neurons. Rapid distension of the esophagus activates both vagal and SLN afferents, and whereas the vagal afferents initiate the central motor program of the belch, the SLN afferents may specifically inhibit the CP by its

Table 10. Effects of vagotomy, SLN, and RLN transection on esophageal distension-induced PS

<table>
<thead>
<tr>
<th>Cm from UES</th>
<th>1</th>
<th>4</th>
<th>7</th>
<th>10</th>
<th>13</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.5 ± 0.1 (10/15)</td>
<td>1.5 ± 0.1 (6/15)</td>
<td>1.6 ± 0.1 (10/15)</td>
<td>1.6 ± 0.1 (10/15)</td>
<td>1.6 ± 0.1 (4/15)</td>
<td>1.7 ± 0.1 (3/15)</td>
</tr>
<tr>
<td>SLN section</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>(0/8)†</td>
<td>(0/8)†</td>
<td>(0/8)†</td>
<td>(0/8)†</td>
<td>(0/8)†</td>
<td>(0/8)†</td>
</tr>
<tr>
<td>RLN section</td>
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<td>NR</td>
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<td>NR</td>
</tr>
<tr>
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<td>(0/3)†</td>
<td>(0/3)†</td>
<td>(0/3)†</td>
<td>(0/3)†</td>
<td>(0/3)†</td>
<td>(0/3)†</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>1.5 ± 0.1 (3/4)</td>
<td>1.5 ± 0.1 (1/4)</td>
<td>1.5 ± 0.1 (1/4)</td>
<td>1.5 ± 0.1 (1/4)</td>
<td>1.5 ± 0.1 (0/4)</td>
<td>1.5 ± 0.1 (2/4)</td>
</tr>
</tbody>
</table>

Values are means ± SE of cm diameter balloon distension. Values in parentheses are number of animals in which the reflex was successfully activated/number of animals in which the reflex was tested. Statistical analyses compared mean values of sensitivities of different reflexes and success rates of activation of pharyngeal swallowing. Student’s t-test was used to test the effects of vagotomy on sensitivities of PS at the esophageal site 1 cm from the UES. Fisher’s exact test was used for all contingency table analyses. †P < 0.05 for a difference from control.

Fig. 13. Diagram of the afferent neural pathways for the EUCR, ELIR, pharyngeal swallow, secondary peristalsis, and belch reflexes. Note that the pharyngeal swallow is mediated only by SLN afferents and the secondary peristalsis is mediated only by vagus nerve afferents. The EUCR, ELIR, and belch are mediated by both the SLN and vagus nerve afferents. Heavy dotted line depicts the junction between the cervical and thoracic cavities. The RLN is an intermediary branch that serves both the vagus nerves and the SLN.
effects on the premotor neurons of the central motor program of the belch. Such a central inhibitory function of SLN afferents may explain the very variable duration of UES relaxation during belching (18) compared with the duration of activation of the other muscles during the belch and compared with the duration of CP relaxation in other upper gut reflexes. The UES relaxation during belching can vary between 0.4 and 6.0 s (18), whereas laryngeal responses, e.g., hyoid bone movement duration (46), during the belch varies less than 1 s. In addition, UES relaxation duration varies more during the belch than other similar brain stem reflexes, e.g., swallowing. That is, whereas UES relaxation during the belch can vary as much as 5.6 s (18), UES relaxation during swallowing varies at most 1 s (6). Therefore, the dual sensory innervation of the belch may allow for a large variation in the amount of air to be expelled by the same reflex response. It is possible that the duration of motor events of the belch other than UES relaxation are also controlled in part by SLN afferents, but this issue has not been investigated.

Although some prior studies have suggested that SLN afferents mediate pseudoaffective responses to nociceptive stimulation of the esophagus (13, 47), our studies show that many of the SLN afferents mediate physiological responses to nonpainful stimuli. In summary, we have found that five upper gut extrinsic reflexes activated from the cervical esophagus are present in the cat. For the first time we have characterized an esophagus-induced activation of pharyngeal swallowing in animals that is most sensitive proximally and have shown that the most proximal esophagus is insensitive to stimulation of secondary peristalsis. These findings may be related to each other. The SLN mediates afferents of the EUCR and ELIR activated from the cervical esophagus. The SLN mediates afferents of the pharyngeal swallowing activated from the entire esophagus but has no role in the activation of secondary peristalsis. The SLN mediates afferents from the esophagus that generate relaxation of the CP during belching, which may allow for varying durations of UES relaxation to account for varying amounts of air to be belched. Therefore, the SLN mediates afferent fibers of many physiological responses to nonnociceptive stimulation of the esophagus.

GRANTS
This work was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases Grant RO1-DK-25731.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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