# Brain Stem Control of the Phases of Swallowing

**Article** *in* Dysphagia · May 2009

Impact Factor: 2.03 · DOI: 10.1007/s00455-009-9211-6 · Source: PubMed

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Dysphagia (2009) 24:333–348
DOI 10.1007/s00455-009-9211-6

REVIEW ARTICLE

# Brain Stem Control of the Phases of Swallowing

**Ivan M. Lang**

**Abstract** The phases of swallowing are controlled by central pattern-generating circuitry of the brain stem and peripheral reflexes. The oral, pharyngeal, and esophageal phases of swallowing are independent of each other. Although central pattern generators of the brain stem control the timing of these phases, the peripheral manifestation of these phases depends on sensory feedback through reflexes of the pharynx and esophagus. The dependence of the esophageal phase of swallowing on peripheral feedback explains its absence during failed swallows. Reflexes that initiate the pharyngeal phase of swallowing also inhibit the esophageal phase which ensures the appropriate timing of its occurrence to provide efficient bolus transport and which prevents the occurrence of multiple esophageal peristaltic events. These inhibitory reflexes are probably partly responsible for deglutitive inhibition. Three separate sets of brain stem nuclei mediate the oral, pharyngeal, and esophageal phases of swallowing. The trigeminal nucleus and reticular formation probably contain the oral phase pattern-generating neural circuitry. The nucleus tractus solitarius (NTS) probably contains the second-order sensory neurons as well as the pattern-generating circuitry of both the pharyngeal and esophageal phases of swallowing, whereas the nucleus ambiguus and dorsal motor nucleus contain the motor neurons of the pharyngeal and esophageal phases of swallowing. The ventromedial nucleus of the NTS may govern the coupling of the pharyngeal phase to the esophageal phase of swallowing.

**Keywords** Swallowing · Oral phase · Pharyngeal phase · Esophageal phase · Reflexive swallow · Deglutitive inhibition · Failed swallows · Central pattern generator · Deglutition · Deglutition disorders

The ingestion of food consists of a set of preparatory events [1, 2], i.e., masticatory sequence, and a set of transport events, i.e., swallowing. The masticatory sequence is composed of three phases [1, 2]: a preparatory phase that transfers food into the oral cavity, a reduction phase that breaks up the food and transfers it to the posterior oral cavity, and a preswallow phase that places the bolus on the tongue and moves the bolus from the oral cavity to the oropharynx. Swallowing also consists of three phases: oral, pharyngeal, and esophageal, each of which transports the bolus across its region and which together moves the bolus from oral cavity to the stomach in one seemingly continuous motion [3]. However, studies have found in adult humans that the muscular movements of the preswallow transport phase of the masticatory sequence are nearly identical to those of the oral phase of swallowing [1]. That is, both movements involve the cyclical alternating contraction of jaw adductor and abductor muscles as well as the suprahyoid muscles. On the other hand, the oral preparatory events of swallowing differ between animals and humans [1, 2], adults and infants [2, 4, 5], and among different species of animals [1, 2]; they undergo significant development changes [4, 5]. Therefore, in this review of the phases of swallowing, only events involved in bolus transport will be considered, and the oral phase of swallowing will be considered physiologically equivalent to the transport phase of mastication.

The individual movements and events that comprise the phases of swallowing have been identified, characterized,

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and reviewed previously [3, 6]. Therefore, this review does not discuss the specific motor events of each phase of swallowing, but it does address the manner in which the sets of motor actions defined as the phases of swallowing are integrated with each other. In addition, while other reviews have assumed the independence of the phases of swallowing, this review provides the evidence for their independence. The independent nature of the phases of swallowing is often difficult to appreciate because of the numerous complex mechanisms that coordinate these phases. This review presents more recent evidence that has revealed a new understanding of the mechanisms of the control and coordination of the phases of swallowing. Swallowing and its coordination are controlled by the central nervous system and there have been many excellent recent reviews on the role of specific brain regions and neurotransmitters in the control of specific motor events of swallowing [7–9]; however, this review concentrates on the role of specific brain areas in the coordination of the phases of swallowing into a coherent physiologic event.

## General Considerations

### Definitions

The normal complete swallow of an adult human consists of three phases: oral, pharyngeal, and esophageal as described below. Under physiologic conditions in normal individuals (except as illustrated below), once initiated all phases of swallowing occur sequentially and they always occur in the same sequence. It is possible to initiate the second or third element of the sequence and when initiated the sequence remains the same. That is, adequate stimulation of the pharynx will initiate the pharyngeal phase as well as the esophageal phase of swallowing, but never the oral phase. Similarly, adequate stimulation of the esophageal phase will never activate the oral or pharyngeal phases of swallowing. Therefore, in this review, when it is stated that in adult humans the oral phase of swallowing has been initiated, it is implied that all phases have been initiated. In addition, in all species under all conditions (except when specifically noted), when the pharyngeal phase of swallowing has been activated, it is implied that the esophageal phase has also been activated.

### Animal Versus Human Studies

As with most areas of physiology, the mechanisms of physiologic processes of swallowing are derived primarily from animal experimentation, but animal experimentation has its limits, as discussed below.

#### *Nature of the Stimulus*

The phases of swallowing can be stimulated either physiologically or nonphysiologically. A physiologic stimulus is one that activates sensory pathways in a manner that occurs naturally. Thus, the injection of water into the pharynx or esophagus constitutes a physiologic stimulus. On the other hand, in animal studies swallowing is often activated using nonphysiologic means that include the electrical or chemical stimulation of nerves or neurons. These nonphysiologic methods are used because in many preparations these are the only methods available to activate the phases of swallowing. Thus, in many studies researchers have stimulated swallowing using the electrical stimulation of various nerves or portions of the brain. While these nonphysiologic stimuli can activate portions of the swallow sequence, none can activate all of the phases and those phases that are activated differ in many ways from physiologically activated phases. Therefore, while studies using nonphysiologic stimuli have provided important information, these differences must always be considered when drawing conclusions from these studies.

The electrical stimulation of the superior laryngeal nerve (SLN) is one of the most often used methods of stimulation of swallowing in animals. SLN stimulation can activate the pharyngeal and esophageal phases of swallowing [10–12], but SLN stimulation has not been compared to stimulation of swallowing using physiologic stimuli in the same animal and preparation; therefore, it is unknown exactly how similar SLN-induced swallowing is to physiologically induced swallowing. Studies in anesthetized [11, 13] or decerebrate [14] cats suggest that SLN stimulation causes responses that differ significantly from physiologically initiated swallows. The SLN provides sensory innervation from portions of the pharynx and larynx [15]; therefore, it probably participates in the initiation of the physiologically activated swallow, but other nerves are also involved [13, 16, 17] and electrical stimulation cannot duplicate the physiologic situation.

#### *Anatomical Differences*

The muscle composition of the esophagus differs among species from smooth to striated muscle. Humans and some animals, e.g., cats, have striated muscle in their upper esophagus and smooth muscle in the lower esophagus, whereas other animals, including rodents and canines, have striated muscle in the entire esophagus [18]. This difference is important with regard to motor nuclei involved in the central control of the phases of swallowing because different brain stem nuclei control smooth and striated muscles of the digestive tract. Therefore, data from animals with purely striated or purely smooth muscle esophagus would not provide appropriate information regarding the motor nuclei controlling the esophageal phase of swallowing in humans.

### *Anesthesia*

Most animal studies are performed under anesthesia and anesthesia significantly alters the phases of swallowing. Afterall, the oral phase, which is initiated voluntarily, does not occur under anesthesia and most anesthetics significantly inhibit the other phases. Therefore, care should be taken when drawing conclusions from studies regarding issues related to the threshold of swallowing stimuli or specific motor or neurophysiologic responses during the phases of swallowing when anesthesia was employed. This is particularly problematic with anesthetics, e.g., ketamine, known to affect receptors involved in swallowing, There is one restraint technique used in animals that allows one to do the more invasive experiments without anesthesia, i.e., decerebration, and this has been shown to preserve function [14] to levels observed in chronic unanesthetized animals or humans. However, since this technique involves the removal of the forebrain, it is only useful in studying the pharyngeal or esophageal phase of swallowing as these phases are entirely controlled by the brain stem.

## Oral Phase of Swallowing

### Definition

The oral phase of swallowing consists of the muscular events responsible for movement of the bolus from the tongue to the pharynx. As described above, in adult humans the ingested material placed on the tongue during mastication is transported to the pharynx by rhythmical alternating contractions of oral and hyoid muscles until the oral phase of swallowing is triggered [1, 2]. The tongue, jaw, and hyoid muscle movements and activities of the triggered oral phase of swallowing are very similar in timing and magnitude (Figs. 1 and 2) to the preceding preswallow rhythmical oral transport events of mastication [19–21]. The preparatory phase of mastication in animals and human infants is absent [4, 5] or short-lasting [21], whereas the primary oral event is the rhythmical transport phase of mastication [1, 2, 21]. These movements are observed (Figs. 1 and 2) as the suck-swallow sequence in human infants [4, 5, 20] or the chew-swallow sequence in animals [19, 21]. In both humans and animals, multiple rhythmical oral events occur for every swallow [1, 2, 4, 5, 19–21]. The great similarity between the oral phase of swallowing and the preswallow transport phase of the masticatory sequence suggests that the same neural circuits control both functions.

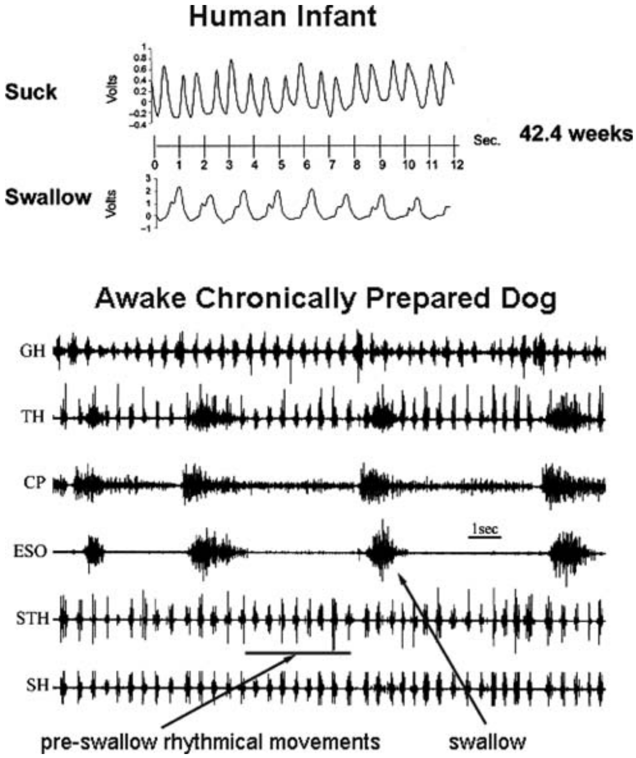

**Fig. 1** Similarity of oral preswallow rhythmical movements with the oral phase of swallowing. *Top* The tracings are voltage outputs from pressure recordings of a human infant of 42.4 weeks gestation during bottle feeding [20]. Note the similarity of the pressure responses during sucking, i.e., oral preswallow rhythmical movements, with the pressure recordings during swallowing. Also note that there are two sucks for every swallow. *Bottom* The EMG tracings from hyoid, pharyngeal, and esophageal muscles in an awake dog while feeding [19]. Note that the preswallow rhythmical movements of all muscles are very similar in timing and magnitude to their responses during the oral phase of swallowing. GH, geniohyoideus; TH, thyrohyoideus; CP, cricopharyngeus; ESO, cervical esophagus; STH, sternothyroideus; SH, sternohyoideus

### Independence of the Oral Phase of Swallowing

In animals [19, 21–23] and human infants [1, 2, 5, 24] the oral phase of swallowing transports ingested material to the pharynx in a repetitive manner, but the pharyngeal phase of swallowing does not occur with each oral phase event (Figs. 1 and 2). The pharyngeal phase of swallowing occurs only after a certain threshold volume or mass of material accumulates in the pharynx. The dependence on peripheral feedback of the initiation of the pharyngeal phase of swallowing was also observed in immature cats. Swallowing initiated by injection of water into the pharynx is associated with the firing of the hypoglossal nerve even in paralyzed adult cats, but in paralyzed kittens this

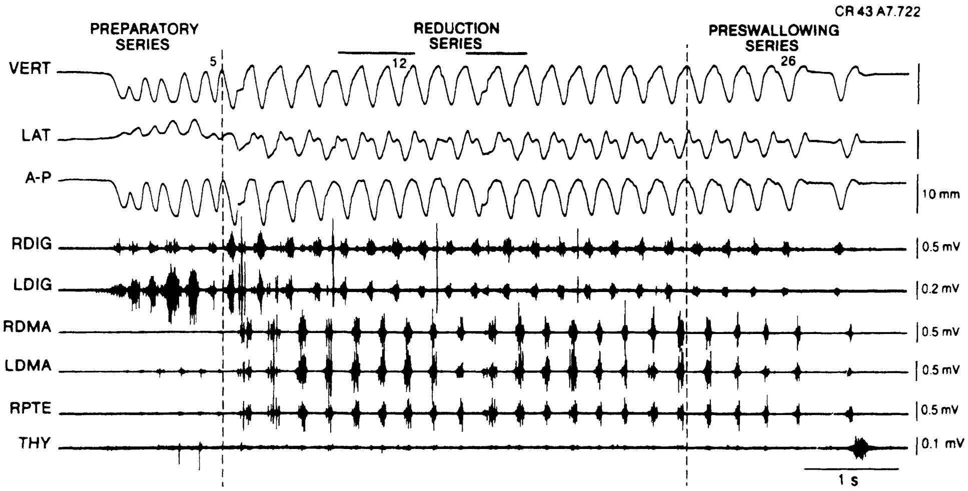

**Fig. 2** Relationship between oral preparatory movements and oral preswallow transport movements in a rabbit during feeding. These tracings are EMG recordings of oral and hyoid muscles and movement of the mandible during feeding in an awake rabbit [21]. Note that the preparatory phase is short and the movements and EMG activities during the swallow are very similar in timing and magnitude to their activities during the preswallow transport period. The swallow is the last response of the series. Movements of the mandible: Vert, vertical; Lat, lateral; A–P, anterior–posterior. EMG of muscles: RDIG, right digastric; LDIG, left digastric; RDMA, right deep masseter; LDMA, left deep masseter; RPTE, right medial pterygoid; THY, thyrohyoideus

response was greatly diminished [25]. Thus, in immature humans and animals, the initiation of the pharyngeal phase of swallowing depends in large part on peripheral feedback. A similar situation also occurs in adult humans, but it is not as easily observed and may not be as dependent on peripheral feedback [1, 2]. During the masticatory sequence in adult humans, the transport phase moves small amounts of ingested material to the pharynx multiple times before the oral phase of swallowing is initiated [1]. When the oral phase occurs it moves the bolus placed on the tongue during the preparatory phase of the masticatory sequence through the oral cavity as well as the pharynx in one smooth motion [1]. Therefore, in animals, infants, or adult humans ingested material is transported to the pharynx before the pharyngeal phase of swallowing is initiated, indicating that the oral phase of swallowing can occur independent of the pharyngeal phase of swallowing.

### Mechanisms of Initiation of the Oral Phase of Swallowing

The oral phase of swallowing is a voluntary event controlled similarly to other complex stereotypic functions like walking. In both cases the event is initiated voluntarily, but the basic underlying rhythm and movements are controlled by pattern-generating neural circuitry. In the case of walking, this circuitry resides in the spinal cord, but for swallowing this circuitry resides in the brain stem as described below (see subsection “Oral Phase of Swallowing” in “Brain Stem Control of the Phases of Swallowing”).

## Pharyngeal Phase of Swallowing

### Definition

The pharyngeal phase of swallowing consists of the events that move the bolus through the pharynx and protects the airway from aspiration. When the bolus reaches the pharynx, it initiates the pharyngeal phase of swallowing that is composed of pharyngeal peristalsis, relaxation of the upper esophageal sphincter, and closure of the glottis [3, 6].

### Independence of the Pharyngeal Phase

The pharyngeal phase of swallowing is independent of both the oral and esophageal phases of swallowing.

#### *Pharyngeal Phase Without the Oral Phase: Reflexive Swallows*

In both humans [26, 27] and animals [10, 14], stimulation of the pharynx can activate the pharyngeal phase of swallowing without activation of the oral phase (Fig. 3); this is sometimes referred to as the pharyngeal or reflexive swallow.

#### *Pharyngeal Phase Without the Esophageal Phase*

The pharyngeal phase of swallowing can occur independent of the esophageal phase of swallowing and has been observed in various ways in humans and animals as described below.

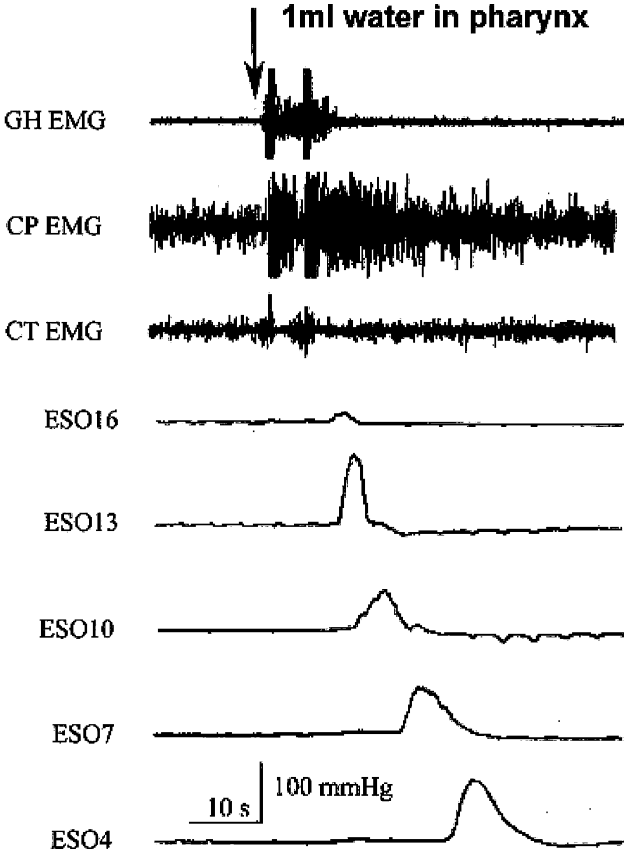

**Fig. 3** Pharyngeal or reflexive swallow. The stimulation of the pharyngeal and esophageal phases of swallowing without the oral phase. These tracings are EMG and manometry recordings in a decerebrate unanesthetized cat in which 1 ml of water was injected into the pharynx [14]. This stimulus initiated the pharyngeal and esophageal phases of swallowing without activating the oral phase. GH, geniohyoideus; CP, cricopharyngeus; CT, cricothyroideus; ESO#, esophagus #cm from the lower esophageal sphincter

*Failed Swallows* The activation of the pharyngeal phase of swallowing without subsequent activation of the esophageal phase occurs in humans, especially during dry swallows; this phenomenon has been referred to as the failed swallow. In humans [28, 29], failed swallows occur 3–4% of the time during wet swallows and 29-38% of the time during dry swallows. Thus, the pharyngeal phase of swallowing is more strongly coupled to the pharyngeal stimulus than the esophageal phase, even though both phases are activated by the pharyngeal stimulus. The central mechanism of this phenomenon is discussed below (see subsection "Failed Swallows" in "Brain Stem Control of the Phases of Swallowing").

*Deglutitive Inhibition* During rapid swallowing sequences [30–32], the esophageal phase of swallowing fails to occur until the last swallow of the sequence (Fig. 4). Evidence suggests that the pharyngeal swallow inhibits the esophageal phase for a short period of time and this prevents two peristaltic waves from occurring in the esophagus at the same time [31, 32]. Considering that the bolus moves far ahead of the peristaltic wave, two peristaltic waves in the esophagus at the same time would be obstructive. This phenomenon also demonstrates that the pharyngeal phase of swallowing is controlled independent of the esophageal phase of swallowing. The central mechanism of this phenomenon is discussed below.

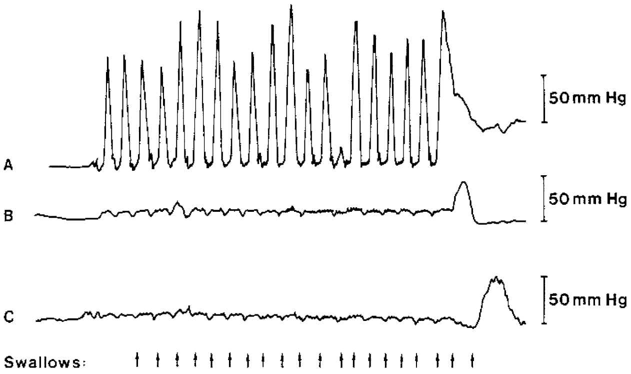

**Fig. 4** Deglutitive inhibition. Manometric recordings of the pharynx and esophagus during a sequence of rapid swallowing [29]. Note that the esophageal phase of swallowing does not occur until the last swallow. **a** Upper esophageal sphincter (UES) pressure. **b** Esophageal pressure 5 cm below UES. **c** Esophageal pressure 10 cm below the UES. Arrows indicate the initiation of a swallow

*Animal Studies* The pharyngeal phase of swallowing can be made to occur in animals [14] without the esophageal phase. In decerebrate unanesthetized cats, when the bolus is diverted such that it does not reach the esophagus, stimulation of swallowing physiologically by injection of water into the pharynx does not lead to the esophageal phase of swallowing (Fig. 5). In anesthetized rats, the pharyngeal phase of swallowing can be selectively initiated by the injection of various neurotransmitter agonists [33–35] into the brain stem. Therefore, the pharyngeal and esophageal phases of swallowing are not controlled by a single set of neurons in the brain and are not one continuous event but two separate events controlled by separate sets of neurons linked together. The central mechanism of this linkage is discussed below (see subsection "Coordination of the Phases of Swallowing" in "Brain Stem Control of the Phases of Swallowing").

## Mechanism of Initiation of the Pharyngeal Phase of Swallowing

The specific sensory stimuli that trigger the pharyngeal phase of swallowing during a normal swallow sequence are unknown. Chemical or mechanical stimuli can activate reflex pharyngeal swallows [27, 36], indicating that activation of either chemo- or mechanoreceptors may be

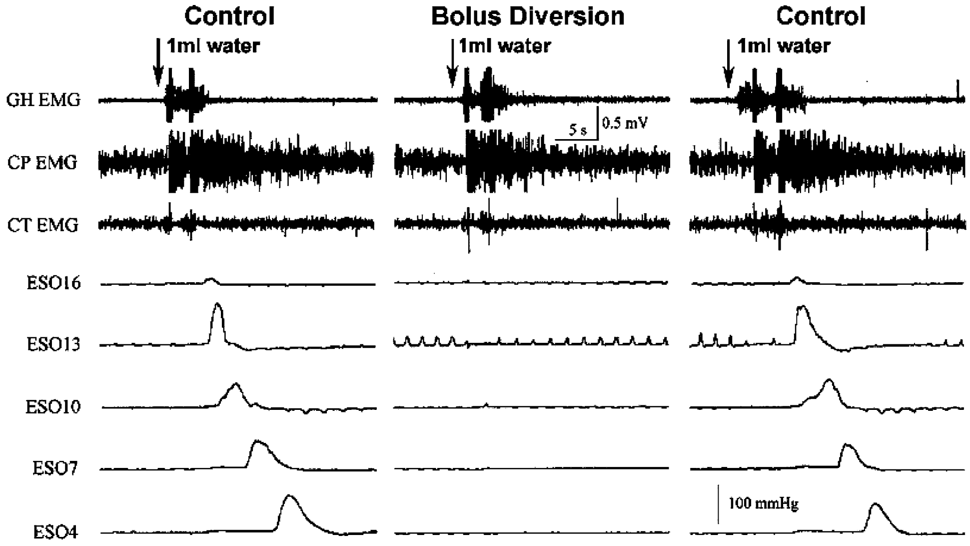

**Fig. 5** The necessity of a bolus for activation of the esophageal phase of swallowing. This figure depicts the effects of diversion of a water bolus from the pharynx on esophageal peristalsis during swallowing. These studies [14] were done in an unanesthetized decerebrate cat with electrodes on pharyngeal muscles and a solid-state manometric catheter in the esophagus. A three-way stopcock was sutured between the pharynx and esophagus at the lower border of the cricopharyngeus muscle. The Control panels depict the effects of switching the stopcock to allow flow from the pharynx to the esophagus. The Bolus Diversion panel depicts the effects of switching the flow from the pharynx to the outside of the body. Bolus diversion prevented the activation of the esophageal phase of swallowing, indicating that esophageal peristalsis even during swallowing is secondary to esophageal stimulation. GH, geniohyoideus; CP, cricopharyngeus; CT, cricothyroideus; ESO#, esophagus #cm from the lower esophageal sphincter

effective, but the role of either in activating physiologic swallows is unknown. Studies in decerebrate cats have found that the most sensitive pharyngeal site for activation of swallowing due to focal pressure is the anterior hypopharynx [37], but the larynx is more sensitive than the pharynx to either chemical or mechanical stimulation [36]. Regardless, it is highly likely that the type and intensity of the physiologic stimulus that activates the pharyngeal phase of the normal swallow may be different or much less intense than that needed to activate the reflex pharyngeal swallow. Afterall, a dry swallow activates the pharyngeal phase 100% of the time, yet a similar stimulus applied to the pharynx is unlikely to activate the reflex pharyngeal swallow. The stimulus of a dry swallow probably includes small changes in pressure, temperature, or chemical composition caused by the small air or saliva bolus and thus may include activation of both mechano- and chemoreceptors. In addition, it is likely that activation of the oral phase facilitates activation of the pharyngeal phase by a central mechanism, but this issue has not been investigated.

The electrical stimulation of the glossopharyngeal or superior laryngeal nerve in animals [11, 16] or the mechanical stimulation of the receptive fields of both nerves in humans [38, 39] can activate the pharyngeal phase of swallowing, but it is unclear what role each pathway plays in triggering the pharyngeal phase of swallowing under physiologic conditions. While the electrical stimulation of these nerves may initiate the pharyngeal phase of swallowing, these stimuli also inhibit the esophageal phase of swallowing [11, 16, 37]; therefore, the manner in which activation of these or other nerves leads to activation of the pharyngoesophageal phase of swallowing under physiologic conditions is unknown.

## Esophageal Phase of Swallowing

### Definition

The esophageal phase of swallowing begins as the bolus reaches the esophagus and continues until the bolus passes through the lower esophageal sphincter. Therefore, this phase consists of contraction of the upper esophageal sphincter, esophageal peristalsis, and relaxation of the lower esophageal sphincter.

### Independence of the Esophageal Phase

The esophageal phase of swallowing is independent of both the oral and pharyngeal phases of swallowing.

#### *Oral and/or Pharyngeal Phase Without the Esophageal Phase*

The ability of the oral or pharyngeal phase of swallowing to occur without a subsequent esophageal phase has been described above.

#### *Esophageal Phase Without the Oral or Pharyngeal Phase*

The esophageal phase of swallowing can occur independent of both the oral and pharyngeal phases of swallowing during secondary peristalsis [3, 6]. That is, distension of the esophagus causes esophageal peristalsis independent of the oral or pharyngeal phase of swallowing.

#### *Primary Versus Secondary Peristalsis*

Reviews of the esophageal phase of swallowing [18] have indicated that there are two types of esophageal peristalsis: primary and secondary. Primary peristalsis is defined as the esophageal peristalsis that occurs during swallowing, thus primary. Secondary peristalsis is defined as esophageal peristalsis that occurs secondary to stimulation of the esophagus, thus secondary. This concept of esophageal peristalsis has persisted for decades despite the fact that there is considerable contradictory evidence. Studies in both cats [14] and dogs [40, 41] have found that esophageal peristalsis does not occur during swallowing when the bolus is diverted from the esophagus. Only one study [42] found that esophageal peristalsis during swallowing persisted after bolus diversion, but these studies did not divert the bolus from the entire esophagus. In these studies the proximal 2 cm of cervical esophagus remained, and as discussed below this difference may have been significant. Therefore, despite the strong persistence of the term primary peristalsis, the literature suggests that there is only one form of peristalsis and it is secondary to esophageal stimulation, whether it occurs during swallowing or not. The central mechanisms that account for this phenomenon are described below (see subsection “Esophageal Phase of Swallowing” under “Brain Stem Control of the Phases of Swallowing”).

### Mechanisms of Initiation of the Esophageal Phase of Swallowing

The specific sensory receptors and afferent pathways that mediate the feedback from the esophagus that activates esophageal peristalsis during swallowing have not been studied directly. Although it is clear that secondary peristalsis can be activated by distension of any part of the esophagus [14, 18], the only study specifically designed to address this issue found that the proximal 2 cm of the esophagus can serve this function [42]. While distension of the esophagus and stimulation of slowly adapting mechanoreceptors acting through the vagus nerves are the routes for activation of secondary peristalsis [14], it has been found that even the air bolus of a dry swallow is sufficient to activate the esophageal phase of swallowing [14]. This finding suggests that receptors other than muscular mechanoreceptors may mediate this function. More recent evidence has shown that proximal few centimeters of the esophagus contains unique receptors and afferent innervation not found in the remainder of the esophagus [43–45]. Receptors particularly sensitive to mucosal stimulation have been found [43–45], and the afferent route from these receptors includes the recurrent laryngeal nerve (RLN) and the superior laryngeal nerve (SLN). It is possible that these mucosal receptors may mediate the afferent feedback that activates the esophageal phase of swallowing.

## **Coordination of the Phases of Swallowing**

The phases of swallowing are coordinated with each other through the central pattern generators and peripheral reflexes. The specific peripheral reflexes that affect the phases of swallowing are discussed below and the pattern generators are discussed in the next section.

### Peripheral Reflex Control of Swallow Coordination

#### *Intraphase Reflexes*

Reflexes of the pharynx and esophagus are critical to the generation of the pharyngeal and esophageal phases of swallowing. As described previously, studies in infants [20, 24] and animals [22, 23] found that the pharyngeal phase of swallowing is not activated as part of the initiation of the oral phase but must be activated by intraphase reflexes, i.e., the presence of the bolus in the pharynx. Deafferentation of the thoracic esophagus [46] in unanesthetized sheep eliminates the esophageal phase at the deafferented region of the esophagus during physiologically activated swallowing. More directly, it was found [14] that the initiation of the esophageal phase of swallowing does not occur as part of prior phases but must be activated by intraphase reflexes, i.e., the presence of the bolus in the esophagus. It has been found [14] in decerebrate nonparalyzed cats that esophageal peristalsis does not occur after stimulation of the pharyngeal phase if the bolus is diverted and never reaches the esophagus. However, even the bolus of air of a dry swallow is sufficient feedback to activate esophageal peristalsis [14].

Therefore, while the central pattern generators set the timing pattern of the phases of swallowing, they do not by themselves produce the motor events of swallowing. Signals generated by the pattern generators must be amplified by peripheral intraphase reflexes that feedback onto the pattern generators producing the specific phase of swallowing.

### *Interphase Reflexes*

There are numerous reflexes of the oral cavity, pharynx, and esophagus that feedback on other areas involved in the phases of swallowing that assist in the coordination and regulation of the swallow sequence.

*Oropharyngeal Reflexes* Studies [47–49] have found that the timing of portions of the oral and pharyngeal phases of swallowing are altered by the oral intake of different volumes of material. Therefore, while there are central pattern generators that set the timing of events, these timing circuits can be adjusted or altered as conditions demand. In this case the oral and pharyngeal pattern generators are altered by reflexes from the oral cavity.

*Pharyngeal Reflexes* Mechanical stimulation of the pharynx inhibits activity of the entire esophagus. The injection of fluid into or mechanical stimulation of the pharynx has been found to inhibit the ongoing esophageal peristalsis [37, 50–52] and to relax the lower esophageal sphincter [50] in animals or humans (Fig. 6). It is likely that this reflex is in part responsible for the phenomenon of deglutitive inhibition [30–32].

*Esophageal Reflexes* The stimulation of the esophagus causes contraction of the cricopharyngeus muscle [53, 54] or closure of the upper esophageal sphincter [55] (Fig. 7). While this effect does not alter the timing of the pharyngeal phase of swallowing, it does affect the magnitude of the pharyngeal response and it may function to help prevent esophagopharyngeal reflux or aspiration.

## Brain Stem Control of the Phases of Swallowing

The central pattern generators, premotor circuitry, and motor neurons controlling the phases of swallowing are contained in the brain stem.

### Swallowing Pattern Generators

Electrophysiologic studies [56–60] have found that neurons of the brain stem contain the timing pattern-generating circuitry that governs the oral, pharyngeal, and esophageal phases of swallowing. One can find neurons that respond at a time delay and duration that corresponds to the expected timing of rhythmical movements of the jaw or peristalsis of the pharynx or esophagus (Fig. 8). These neural events are not caused by feedback from the periphery, e.g., propagating peristalsis, because this pattern persists even in paralyzed animals [56]. Therefore, these neural events found in premotor neurons must control the timing of these phases of swallowing. These pattern generators not only govern the timing of the motor responses of each phase of swallowing, but also govern the timing between phases of swallowing as described below (see subsection "Between Phase Coordination" under "Coordination of the Phases of Swallowing").

### Oral Phase of Swallowing

Swallowing is initiated by a voluntary act but much of this process is composed of stereotyped motor activity that is controlled by brain stem central pattern generators. These central pattern generators not only function to control the

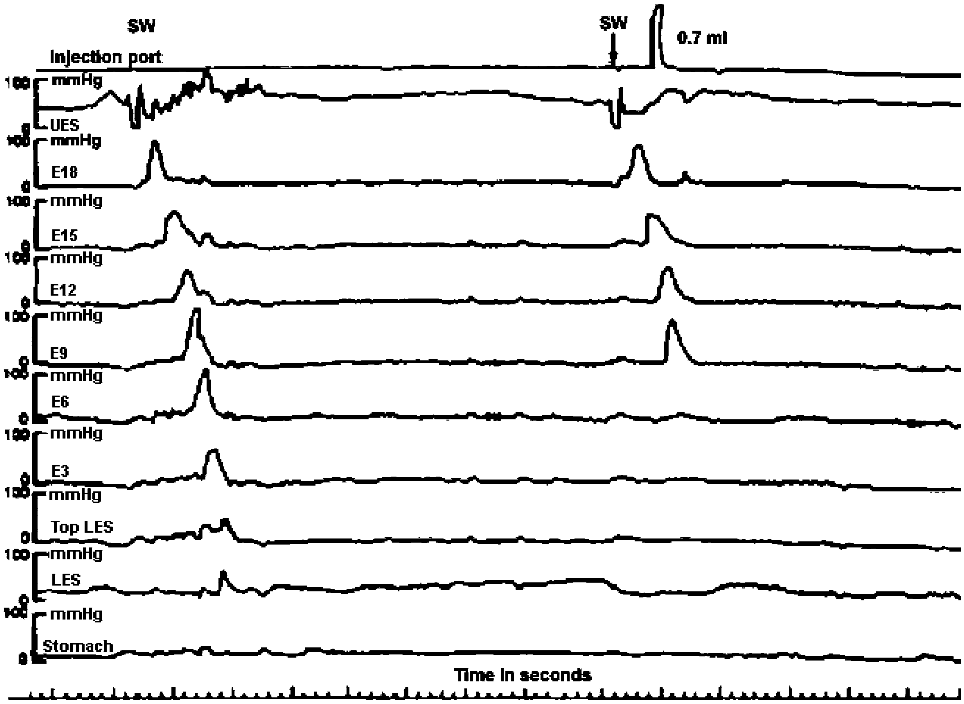

**Fig. 6** The pharyngoesophageal inhibitory reflex. This figure depicts manometric recordings from the pharynx, esophagus, and stomach of a human during swallowing [51]. The first response is the control manometric response during a voluntary dry swallow. During the second swallow, 0.7 ml of water was injected into the pharynx when the peristaltic wave had entered the proximal esophagus. Pharyngeal stimulation blocked the progression of the esophageal phase of swallowing. LES, lower esophageal sphincter; E#, esophagus #cm above the LES; UES, upper esophageal sphincter, SW, swallow

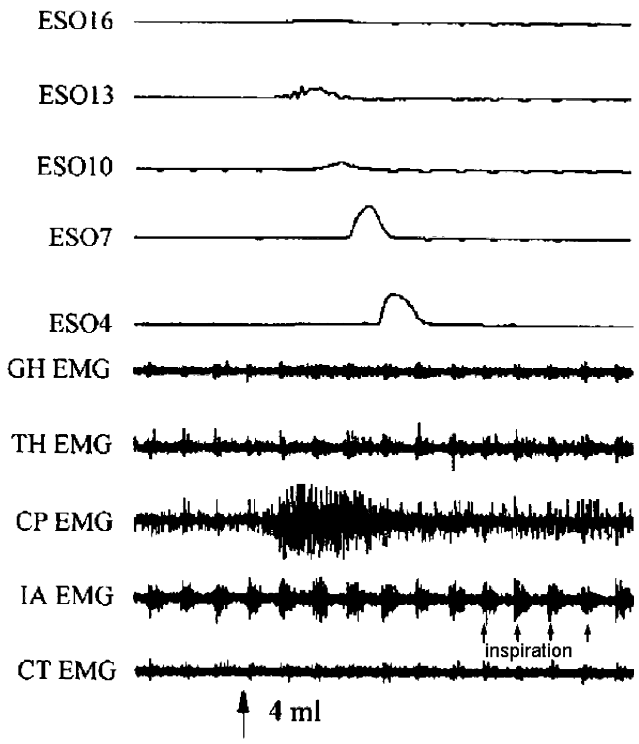

**Fig. 7** Esophago-UES contractile reflex. This figure depicts the EMG and manometric recordings of the pharynx and esophagus in a cat during distension of the esophagus with air [14]. Distension of the esophagus with 4 ml of air increased EMG activity of only one muscle of the pharynx, i.e., the cricopharyngeus muscle (CP, the primary closing muscle of the upper esophageal sphincter) and activated secondary peristalsis. The CP response preceded the activation of secondary peristalsis. GH, geniohyoideus; TH, thyrohyoideus; CP, cricopharyngeus; IA, interarytenoideus; CT, cricothyroideus; ESO#, esophagus # cm from the lower esophageal sphincter

pharyngeal and esophageal phases of swallowing but also the portions of the oral phase of swallowing. The anencephalic infant exhibits rhythmical oral movements and can swallow [61, 62]; therefore, oral transport events defined in this review as the oral phase of swallowing are controlled by subcortical structures. In addition, cortical neural stimulation in animals causes the rhythmical movement of oral muscles that resembles that observed during the preparatory phase of ingestion [63, 64]. These movements as explained above not only break up the food but can also transport the bolus from the tongue to the pharynx. The electrical stimulation of the cortical swallowing area activates neurons [59, 60, 63–65] within the reticular formation and vestibular nucleus, and when activated these neurons exhibit rhythmical excitation (Fig. 9) similar to that observed in the oral muscles [60, 63, 64]. Therefore, neurons of the trigeminal nucleus and reticular formation probably comprise the neural circuitry that govern the stereotyped oral movements that occur during the oral phase of swallowing.

## Pharyngeal Phase of Swallowing

### *Premotor Nuclei*

In decerebrate unanesthetized cats [66], the pharyngeal phase of swallowing activated physiologically by the injection of water into the pharynx (Fig. 10) is associated with activation of premotor neurons in the intermediate (NTSim), ventromedial (NTSvm), and interstitial (NTSis) subnuclei of the NTS. The NTSis and NTSim have also been found to be associated with swallowing activated by electrical stimulation of the SLN [67] or RLN [68] in the anesthetized rat. Using retrograde tract-tracing studies, it was found that the NTSis and NTSim project to the pharyngeal muscles [69–71] in a pathway consisting of two synapses. In addition, the electrical [34] or chemical [33, 35] stimulation of this region of the NTS causes activation of the pharyngeal phase of swallowing, and neurotransmitter antagonists microinjected into this region [33–35] block the pharyngeal phase of swallowing. Therefore, the primary NTS premotor subnuclei that control the pharyngeal phase of swallowing are the NTSis and NTSim.

The only difference in results between the cat and the rat studies of the NTS subnuclei involved in the pharyngeal phase of swallowing discussed above is the involvement of the NTSvm. This difference may be due to technical differences between the physiological studies or the limitations of these histologic studies. The NTSvm may be more than two synapses away from the pharyngeal muscles and therefore it would not have been disclosed by the specific tract-tracing technique used in rats [69–71]. In addition, the NTSvm may not at all connect with the pharyngeal muscles, but it still might be a very important part of the pharyngeal phase of swallowing. This issue is discussed in more detail below.

### *Motor Nuclei*

In unanesthetized decerebrate cats, the pharyngeal phase of swallowing (Fig. 10) is associated with activation of motor neurons in the caudal dorsal motor nucleus (DMN) and dorsal nucleus ambiguus (NA) [66]. The neurons activated during the pharyngeal phase of swallowing in the DMN were significantly smaller than those activated during the esophageal phase of swallowing. These neurons may be inhibitory rather than excitatory because the smaller neurons of the DMN are interneurons and the larger neurons are motor neurons [72] and interneurons are often inhibitory. Considering that pharyngeal stimulation inhibits esophageal peristalsis [37, 48, 49], these DMN interneurons activated by pharyngeal stimulation may be inhibitory and therefore may mediate the pharyngoesophageal inhibitory reflex (Fig. 8) and the inhibition of the esophageal phase by the pharyngeal phase of swallowing. Rat studies

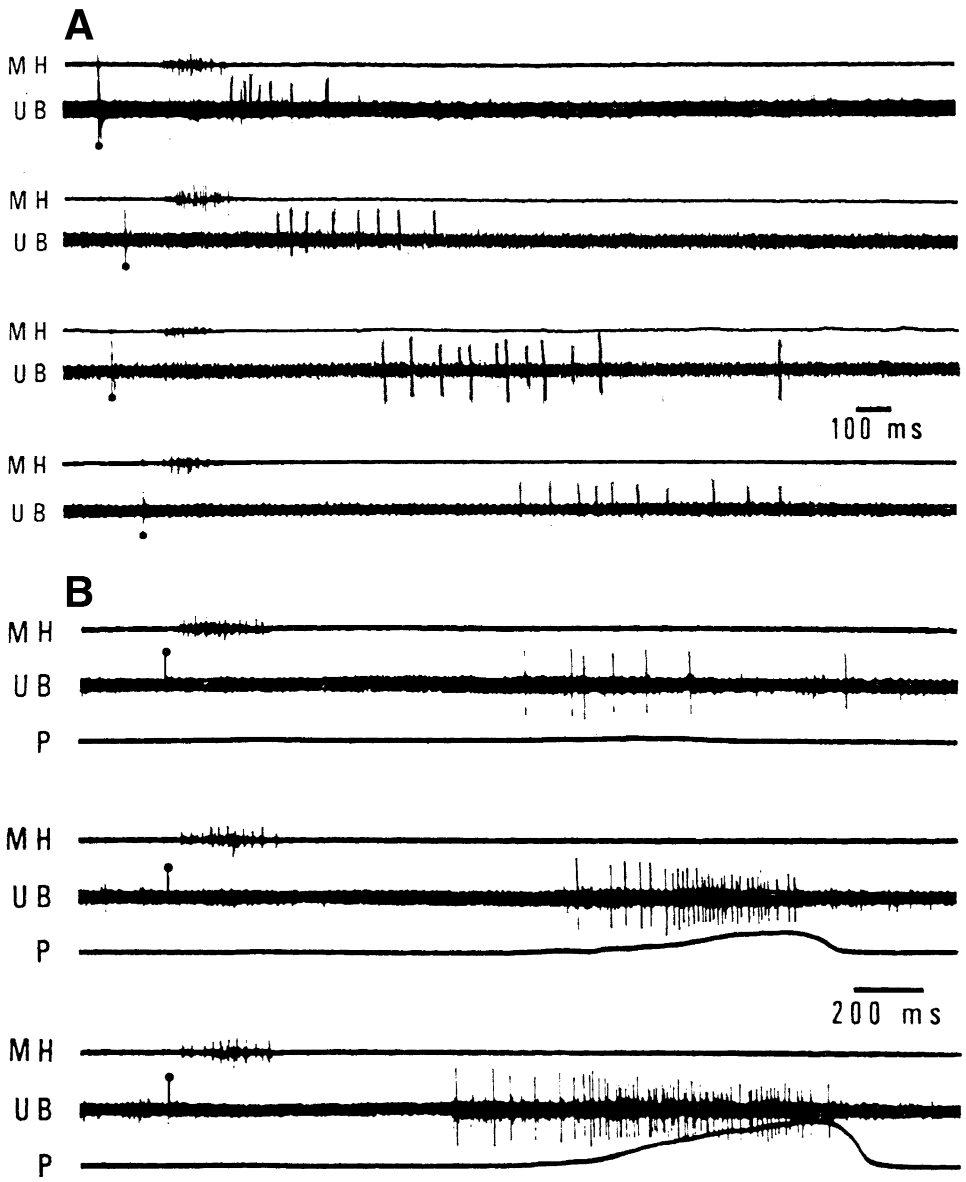

**Fig. 8** The recording of brain stem unit activity during swallowing and the effects of distension of the esophagus. **a** Esophageal pattern generator neuronal activity. The activity of various neurons on the brain stem after activation of swallowing by stimulation of the superior laryngeal nerve [56]. Note the increase in unit activity that occurs in groups at different delays from the beginning of swallowing as indicated by activation of the mylohyoideus. The delays of activation of these neurons are similar to the delays of occurrence of esophageal peristalsis. **b** Peripheral feedback excitation of pattern generator neurons. The top tracing depicts the control condition of the activation of a brain stem unit after the initiation of swallowing by stimulation of the superior laryngeal nerve [56]. The second and third tracings depict the effects of distension of the esophagus on the firing of this unit. Note that esophageal distension greatly increased the activation of the brain stem unit during swallowing, and the greater the pressure increase the greater the unit response. MH, mylohyoideus EMG; UB, brain stem unit activity; P, pressure

have not found the DMN to be involved in swallowing [69, 73, 74], but this is probably due to species differences. The rat esophagus is all striated muscle and the DMN is the motor nucleus of digestive tract smooth muscle [18].

The pharyngeal phase of swallowing is associated with activation of neurons in the dorsal NA (NAd) in the unanesthetized cat [66]. Tract-tracing studies in cats [75, 76] and rabbits [77] have found the NAd to be the location of the motor neurons of the pharyngeal muscles. The organization and nomenclature of the NA of the rat is different from that of the cat. The rat NA has compact and subcompact subnuclei rather than dorsal and ventral, and the rat NA subnucleus that contains the pharyngeal motor neurons is the Nasc, which is located ventrally not dorsally [73, 78].

## Esophageal Phase of Swallowing

### *Premotor Nuclei*

The esophageal phase of swallowing activated by a physiologic stimulus in unanesthetized cats (Fig. 10) is associated with activation of premotor neurons [66] in the central (NTSce), ventral (NTSv), dorsolateral (NTSdl), and ventrolateral (NTSvl) subnuclei of the NTS. In addition, neurons of the NTSv and NTSvl have been found to be excited during SLN stimulation-induced swallowing in anesthetized sheep. Tract-tracing studies in rats have found that of all the NTS subnuclei, only the NTSce projects to the esophagus within two synapses [69, 71]. In addition, the electrical [79] or chemical [33, 34, 79, 80] stimulation

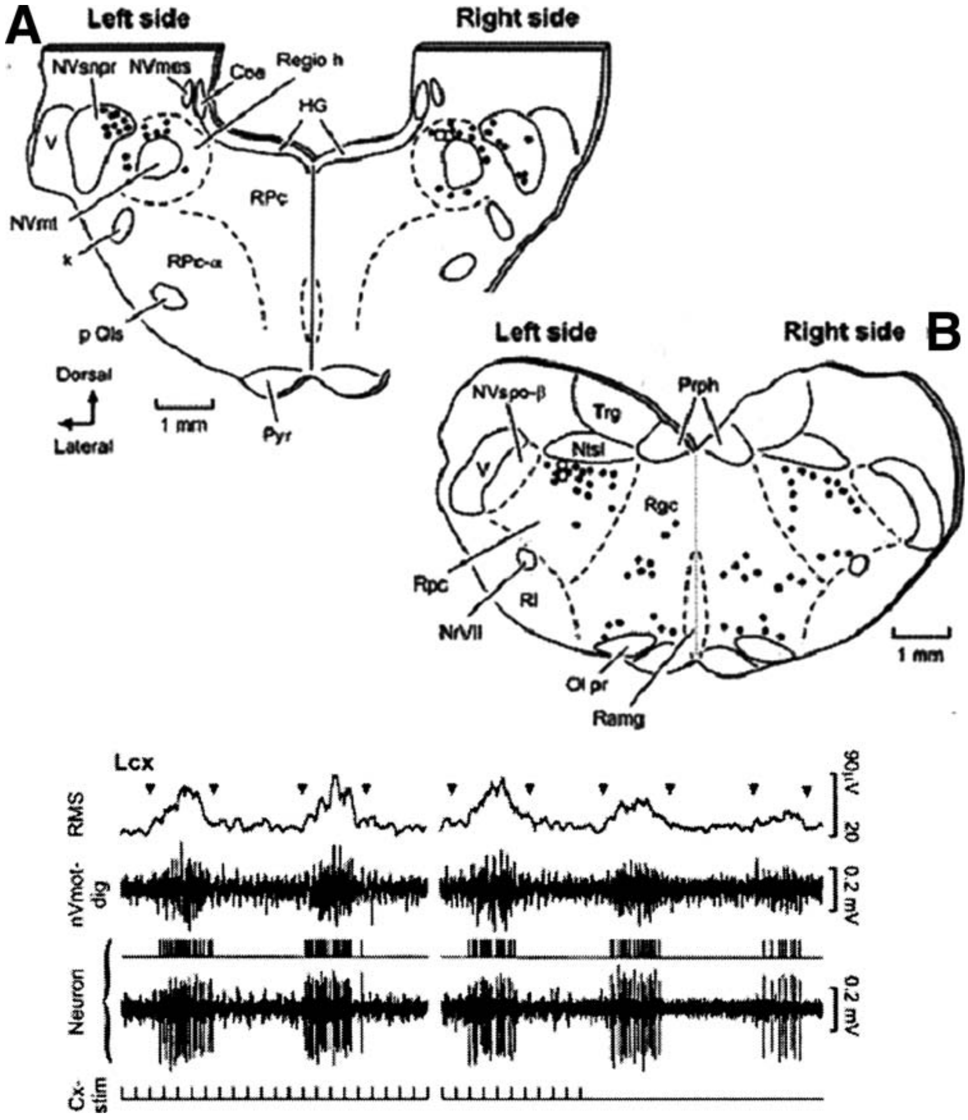

**Fig. 9** Brain nuclei involved in the oral phase of swallowing. *Top* The brain stem nuclei activated during oral events stimulated by electrical stimulation of the cortical mastication area (CMA) in the rabbit [65]. Black dots indicate location of activated neurons. **a** Trigeminal nucleus. **b** Reticular formation. NV, trigeminal nucleus; RP, pontine reticular formation; HG, central gray matter; Pyr, pyramid tract. Note that CMA stimulation primarily activates neurons in the trigeminal nucleus and reticular formation. *Bottom* The effects of CMA stimulation on the firing of units within the pontine reticular formation of the rabbit [59]. Note that the rhythmical activation of the reticular formation unit corresponds to the rhythmical discharge of the trigeminal motor unit of the digastric muscle during stimulation of the cortex. This same stimulation also activates the rhythmical preswallow oral motor responses during the masticatory sequence. Vmotor-dig, trigeminal nucleus motor neuron of the digastric muscle; Cx, cortical stimulation; RMS, root mean squared of motor unit

of the region of the NTSce initiates the esophageal but not the pharyngeal phase of swallowing, and the microinjection of neurotransmitter antagonists [33, 34, 79] or the creation of a lesion in this area [80] blocks the esophageal but not the pharyngeal phase of swallowing. Therefore, the primary premotor nucleus involved in the control of the esophageal phase of swallowing is probably the NTSce.

While the NTSce may be the primary premotor subnucleus controlling the esophageal responses during esophageal phase of swallowing, other subnuclei may mediate other responses associated with the esophageal phase of swallowing. There may be very significant neurons activated during the esophageal phase of swallowing that are either more than two synapses from the esophagus or have no connection at all to the esophagus. For example, there are many physiologic connections between the esophagus and respiratory system: There are numerous esophagorespiratory tract reflexes [81–83]. Swallowing causes resetting of respiratory drive [84, 85], and the primary termination sites of afferents from the respiratory tract include the NTSv, NTSvl, and NTSdl [69, 86]. Therefore, it is likely that the nuclei, other than the NTSce, activated during physiologic activation of the esophageal phase of swallowing may be related to respiratory responses that occur during activation of this phase of swallowing.

### *Motor Nuclei*

The motor neurons of the esophageal phase of swallowing activated by physiologic stimuli in unanesthitzied cats [66] are located in the both rostral (DMNr) and dorsal (DMNc) subnuclei nuclei of the DMN, but primarily in the DMNr. These neurons in both subnuclei are significantly larger than those activated during the pharyngeal phase of swallowing, reflecting their nature as motor neurons [72]. This finding is corroborated by tract-tracing studies in cats [75].

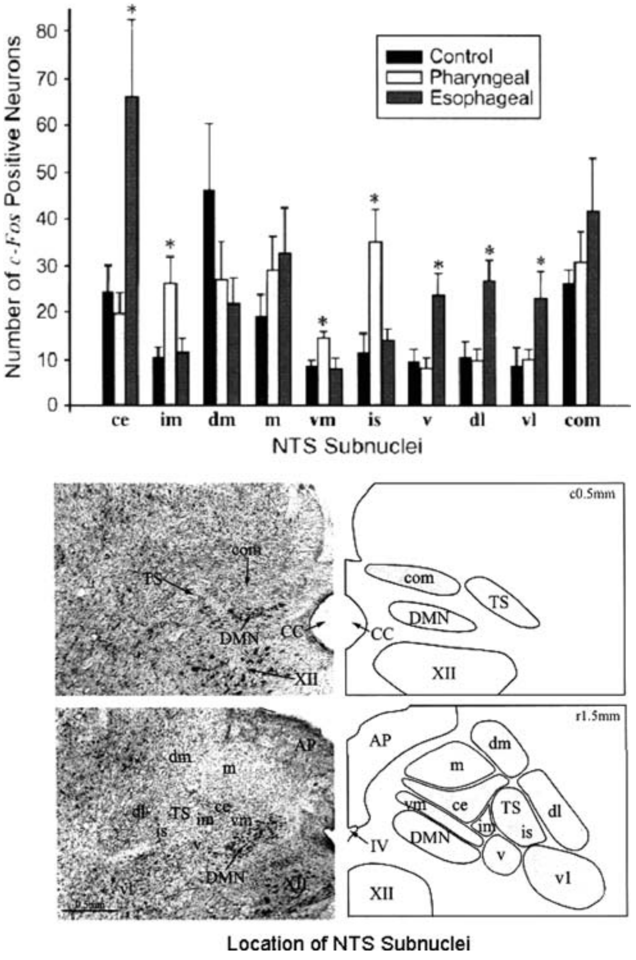

**Fig. 10** The effects of the pharyngeal or esophageal phase of swallowing on activation of specific subnuclei of the nucleus tractus solitarius (NTS) and the location of these subnuclei in the brain stem. The graph depicts the magnitude of the response of the specific NTS subnuclei to activation of the pharyngeal and esophageal phases of swallowing and the diagram depicts the location of these subnuclei in the brain stem. The phases of swallowing were selectively stimulated once per minute for 3 h in unanesthetized decerebrate cats [66]. The pharyngeal phase was associated with activation of the intermediate (im), ventromedial (vm), and interstitial (is) subnuclei of the NTS. The esophageal phase was associated with activation of the central (ce), ventral (v), dorsolateral (dl), and ventrolateral (vl) subnuclei of the NTS. These subnuclei are the second-order sensory neurons as well as the neurons that contain the central pattern generators of the pharyngeal and esophageal phases of swallowing. dm, dorsomedial nucleus; m, medial nucleus; com, commisural nucleus; AP area postrema; XII, hypoglossal nucleus; DMN, dorsal motor nucleus; TS, tractus solitarius

It is likely that the DMNr neurons are involved in excitatory responses whereas the DMNc neurons are involved in inhibitory responses of the esophagus during the esophageal phase of swallowing. Lower esophageal sphincter (LES) motor neurons of the DMNr have been associated with LES contraction [86], whereas DMNc neurons have been associated with LES relaxation [87, 88]. During the esophageal phase of swallowing, the LES first relaxes then contracts, therefore, the excitation of both subnuclei during the esophageal phase of swallowing is expected.

In studies of SLN-induced swallowing in mice [67], it was found that both the DMNr and the DMNc were activated equally, rather than preferentially by the DMNr. This difference probably reflects the anatomical difference in muscle composition of the esophagus between rodents and cats or humans. The DMN primarily contains the motor neurons of the smooth muscle esophagus and rodents have only smooth muscle in their LES whose motor neurons are located in the DMN. Therefore, because the DMNr contains excitatory motor innervation for the entire smooth muscle esophagus in cats but only the LES in rodents, and the only inhibitory innervation of the esophagus in either cats or rodents is that to the LES from the DMNc, it is not unexpected that the during the esophageal phase of swallowing the DMNr of cats would have more units activated than DMNc.

The ventral portion of the NA has been found to be activated primarily during swallowing initiated by a physiologic stimulus in cats [66]. This is consistent with histologic studies that found that the motor units of the striated-muscle esophagus in cats [75] or rabbits [76] are located in the NAv, and the esophageal premotor nucleus, NTSce, connects directly with the NA [71, 88]. The esophageal motor units of rats have been found in the dorsal portion of the NA (NAc), but this difference from cats probably reflects the anatomical differences between species. The NAc in rats has been found to contain motoneurons of the esophagus, and these neurons were excited during swallowing by chemical stimulation of the dorsal medulla [89]. The chemical stimulation of the NA in rats causes either synchronous or propulsive esophageal contractions, and direct chemical stimulation of NAc neurons in vitro results in rapid membrane depolarization and spiking [89]. Therefore, the motor nucleus of the striated muscles of the esophageal phase of swallowing is the NA, and given that the human esophagus is more similar to that of the cat than the rat, the specific subnucleus in humans is probably the NAv.

## Coordination of the Phases of Swallowing

### *Role of Peripheral Feedback to the Brain Stem*

The timing pattern of activity reaches the pharyngeal motor neurons at levels strong enough to activate the pharyngeal muscles, but not strong enough to activate esophageal peristalsis without feedback from the periphery. During SLN-induced or pharyngeal-induced swallowing with no bolus or lack of peripheral feedback, the pharyngeal premotor [56, 90, 91] and motor [57] neurons are strongly activated, but the esophageal premotor [56, 90] and motor [57, 58] neurons fire weakly, and the esophageal premotor neurons associated with more distal areas of the esophagus fire weakest [56, 90]. When these premotor [56, 90] or motor [92] neurons are recorded during SLN-induced swallowing with sensory feedback intact, the unit activity of these neurons is excited somewhat by distension of the corresponding area of the pharynx [56, 90], but the esophageal neurons are greatly excited [56–58, 90, 92] (Fig. 8b). That is, the presence of a bolus feeds back onto the corresponding pattern-generating neurons of the NTS and excites them, especially the esophageal premotor neurons, many times above the basal level of activity. Therefore, these neurophysiologic studies suggest that while feedback from the periphery to the premotor neurons is not necessary to produce the timing pattern of the pharyngeal and esophageal phases of swallowing, the output to the motor neurons and the motor response of these phases of swallowing, especially the esophageal phase, are strongly dependent upon feedback from the periphery.

### *Within-Phase Coordination*

All phases of swallowing are composed of the sequential activation of muscles to produce bolus transport. The mechanism generating this sequencing has been studied only for the esophageal phase of swallowing, but this mechanism may also apply to other phases of swallowing. During the esophageal phase of swallowing, activation of premotor neurons associated with the proximal esophagus inhibits premotor neurons associated with the distal esophagus [56]. This inhibitory response is followed by excitation [56, 93]. Thus, the polarization of the inhibitory drive of premotor neurons from more proximal structures onto premotor neurons of more distal structures guarantees not only that the more proximal structures are connected to the more distal structures, but that this activation progresses only in one direction. Furthermore, the distal inhibition delays activation of the more distal structures, and this series of delays forms the temporal sequence. Thus, when swallowing is activated, it always moves distally in sequence within each phase.

### *Between-Phase Coordination*

Although the pharyngeal and esophageal phases of swallowing are controlled by separate and independent structures and pathways, these phases are coordinated with each other to ensure efficient movement of the bolus. This coordination involves both excitatory and inhibitory mechanisms. In anesthetized sheep, activation of the pharyngoesophageal swallow by SLN stimulation activates pharyngeal premotor neurons simultaneous with inhibition of esophageal premotor neurons [56], and pharyngeal distension [93] inhibits esophageal premotor neurons. This inhibition is also manifested as hyperpolarization of esophageal motor neurons of the NA. Thus, the initial coordinating action is inhibition of the esophageal phase that allows an appropriate time delay between these phases to accommodate bolus movement. The initial inhibition is soon followed by excitation of the esophageal premotor neurons, depolarization of the esophageal motor neurons, and contraction of the esophagus.

Evidence suggests that the NTSvm may participate in this coupling process. The NTSvm is activated during the pharyngeal but not the esophageal phase of swallowing in decerebrate cats [66]; therefore, its activation is not part of the esophageal phase of swallowing. In addition, prior studies have found that the electrical [79] or chemical [33, 34, 79, 80] stimulation of an area identified as the NTSce, but which is adjacent to and possibly within the NTSvm, initiates the esophageal but not the pharyngeal phase of swallowing. Also, the microinjection of neurotransmitter antagonists [33, 34, 79] into or lesions [94] of this area blocks the esophageal but not the pharyngeal phase of swallowing. While this area was defined as the NTSce, many of the sensitive sites were between the NTSce and the DMN, the location of the NTSvm. The NTSvm was only recently identified [66] so prior authors could not make this distinction. Regardless, the area of the ventral portion of the NTSce or the NTSvm may function to couple the pharyngeal and esophageal phases of swallowing.

### Failed Swallows

Studies in anesthetized [56, 95, 96] and unanesthetized [57, 58] animals found that during SLN-induced [56, 95, 96] or physiologically activated [57, 58] swallows, pharyngeal premotor [56, 95, 96] or motor neurons [57, 58] discharge at a higher rate than those of the esophageal premotor neurons. While pharyngeal stimulation increases pharyngeal premotor neuronal discharge somewhat [56], esophageal stimulation greatly increases esophageal premotor discharge [56, 95]. On the other hand, elimination of sensory afferent feedback does not significantly reduce the discharge of the pharyngeal premotor neurons [91], but it does significantly reduce the discharge of the esophageal premotor [56, 95] and motor [46, 56, 80] neurons. Therefore, the pharyngeal premotor neurons, once activated, do not require peripheral stimulation to attain near maximal output, whereas the esophageal premotor neurons require significant sensory afferent feedback to maintain activation. This neurophysiological arrangement probably accounts for the lack of failed pharyngeal phases during swallowing but the common occurrence of failed esophageal phases during swallowing.

### Deglutitive Inhibition

The mechanism of deglutitive inhibition has been investigated in animals. Studies in anesthetized animals found that SLN stimulation-induced swallowing [56, 95, 96], or mechanical stimulation of the pharynx [97], inhibited esophageal premotor neurons of the NTS [56, 95–97] or esophageal motor neurons of the NA [89, 97, 98]. In addition, stimulation of pharyngeal premotor neurons in rat brain slice preparation [80] hyperpolarizes esophageal motor neurons of the nucleus ambiguus (NA). Therefore, deglutitive inhibition may be an inherent part of the brain circuitry that controls the pharyngeal and esophageal phases of swallowing.

## Summary

The phases of swallowing are independent of each other and the stereotypic movements of each are controlled by pattern-generating circuitry of the brain stem. The oral phase of swallowing is initiated voluntarily and the pharyngeal and esophageal phases of swallowing occur secondary to stimulation of the pharynx and esophagus by the bolus through intraphase reflexes. Intra- and interphase reflexes also alter or modify the other phases of swallowing to account for variations in physiologic functions. These variations include the reflexive swallow, failed swallow, deglutitive inhibition, and secondary peristalsis. The central pattern generators for the stereotypic motor transport patterns of the oral phase of swallowing are located in the reticular formation and trigeminal nucleus. The central pattern generators for the pharyngeal and esophageal phases of swallowing are located in the nucleus tractus solitarius.

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