Brain Stem Control of Swallowing: Neuronal Network and Cellular Mechanisms

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I. Introduction

The act of swallowing is a fundamental motor activity in mammals, since it serves two vital functions. By propulsing food from the oral cavity into the stomach via the pharynx and the esophagus, swallowing subserves an alimentary function and thus constitutes the first, irreversible step in feeding behavior. The swallowing reflex also protects the upper respiratory tract by cleaning the naso- and oropharynx and closing the nasopharynx and the larynx, to prevent the pulmonary aspiration of food particles (34, 87, 90, 110, 226, 248).

Swallowing is known to be a complex but stereotyped motor sequence, with the implication that it involves a fixed behavioral pattern. It constitutes, however, one of the most elaborate motor functions, even in hu-
mans, since it requires coordinating an extraordinary bilateral sequence of activation and inhibition among more than 25 pairs of muscles in the mouth, pharynx, larynx, and esophagus (70, 87, 226). One of the most striking characteristics of swallowing is that the motor sequence can be readily initiated by stimulating a nerve, namely, the internal branch of the superior laryngeal nerve (SLN) (61, 87, 149, 225, 279). Swallowing therefore probably constitutes, as Doty (87) has said, one of “the most complex stereotyped pattern of behavior that can be consistently evoked by electrical stimulation of a peripheral nerve.” Because the motor event elicited by stimulating the SLN includes all the components of the physiological motor pattern, swallowing provides a suitable model for studying the neurophysiological mechanisms underlying motor pattern generation.

Since Magendie (208), the act of swallowing has generally been described as having three phases or stages (34, 51, 70, 87, 89, 226). As regards the motor pattern occurring during feeding behavior, swallowing has been subdivided into an oral, preparatory phase, followed by a pharyngeal phase, and then by an esophageal phase, corresponding to the primary peristalsis of the esophagus (78, 110, 142, 164, 280). In fact, the oral, preparatory phase during which the alimentary bolus is formed is almost entirely voluntary and can be interrupted at any time, whereas the pharyngeal and esophageal phases are involuntary. Moreover, once it has been initiated, the pharyngeal phase of swallowing constitutes an irreversible motor event. The same irreversible motor sequence is observed both during the swallowing, which is not associated with food consumption, but serves to clear the oropharynx of small amounts of saliva, and during the reflex swallowing elicited by stimulation of the SLN (87). Under these swallowing conditions, the pharyngeal phase of deglutition involves not only pharyngeal and laryngeal muscles, but also muscles in the oral cavity such as the tongue and suprahypoid muscles. Therefore, the actual motor event of swallowing can be best described as being composed of an oropharyngeal stage and a subsequent esophageal stage. It is this overall motor pattern, corresponding to the basic or fundamental swallowing, which has been mainly studied in neurophysiological investigations (154–156).

Classically, swallowing has been taken to be a sequential motor event and not a rhythmic motor behavior like mastication, respiration, or locomotion. Deglutition can occur repeatedly during feeding, but this is generally regarded as simply involving the repetition at a low frequency of a single sequential motor performance (87, 164, 194). However, under the appropriate stimulus, some components of the swallowing act can take on the properties of a rhythmic motor behavior (51, 87, 149, 161, 279). A typical rhythmic pattern of swallowing is elicited during long-lasting repetitive stimulation of the SLN. Thus swallowing is a suitable model not only for the neurophysiological analysis of sequential motor events, but also for that of rhythmic motor behaviors. However, it should be stressed that the rhythmic motor pattern is mainly associated with the oropharyngeal phase of swallowing, and the uppermost part of the cervical esophagus when the rhythmic frequency is low. No esophageal peristalsis occurs during the successive oropharyngeal sequences, and only the last oropharyngeal event in the series is followed by the complete esophageal stage (79, 111, 279, 350, 353).

In mammals, all the muscles involved in the oropharyngeal stage are striated and are therefore driven by several pools of motoneurons located in various cranial motor nuclei in the brain stem and the uppermost levels of the cervical spinal cord (51, 87, 156, 226). The esophageal muscle is entirely composed of striated fibers in species such as rat, guinea pig, rabbit, dog, sheep, and cow and is therefore controlled by cranial motoneurons. In some species however, e.g., cats, opossums, and primates, a variable portion of the lower esophagus is composed of smooth muscle fibers, controlled by the autonomic nervous system (60, 79, 110, 111, 280).

It has by now been clearly established, as originally postulated in the pioneering work by Meltzer (218–220), that the sequential and rhythmic patterns of swallowing are formed and organized by a central pattern generator (CPG). The CPG was previously described as a swallowing center that can be subdivided into three systems: an afferent system corresponding to the central and peripheral inputs to the center; an efferent system corresponding to the outputs from the center, consisting of the various motoneuron pools involved in swallowing; and an organizing system corresponding to the interneuronal network that programs the motor pattern (51, 87, 156, 280). In fact, the concept of a swallowing center implies the idea of an anatomical localization, whereas that of a CPG is based on a more functional principle focusing on the activity of the various pools of neurons, i.e., motoneurons and interneurons, involved in the motor activity. The swallowing CPG is located within the medulla oblongata (156, 161). Swallowing is indeed a primitive reflex, which means that it is present in all animals with organs serving differentiated functions and that it emerges early during development. The normal human fetus can swallow by the 12th gestational week, before the cortical and subcortical structures have developed (139). It has also been reported that swallowing is still possible in human anencephalic fetuses (266, 269). Experimental studies have shown, moreover, that the destruction of several nervous structures such as the forebrain, cerebellum, and pons does not alter swallowing (34). In fact, the basic sequential motor pattern seems to remain nearly normal as long as the nervous structures located between the Cl level and the trigeminal motor nuclei are intact (86, 89, 150, 152, 231).
Swallowing, which can be triggered by stimulating a peripheral nerve and involves limited regions of the central nervous system, is an attractive model for the neurophysiological analysis of sequential and rhythmic motor behaviors. However, it has received less attention than other fundamental motor activities such as locomotion, mastication, or respiration (65). This is probably due to the complexity of the motor pattern along with the great number of muscles and cranial nerves involved, which renders neurophysiological studies difficult. In addition, the whole swallowing sequence is difficult to initiate in anesthetized animals (149, 152).

Since the extensive review by Doty (87), several reviews on swallowing and its various aspects, such as those relating to esophageal motility, have been published (51, 70, 72, 78, 79, 84, 90, 110, 111, 129, 132, 154–156, 161, 164, 226–228, 278, 280, 353). However, the brainstem mechanisms contributing to the sequential and rhythmic motor events involved in swallowing have not been analyzed so far in detail. This review therefore focuses on the brain stem CPG responsible for swallowing. It deals with the results obtained over the last 25 years, first using classical electrophysiological techniques and then pharmacological approaches, as well as neuroanatomical methods, such as tract-tracing techniques. These results have been mainly obtained on anesthetized or decerebrated animals, and in some cases on in vitro brain stem slices. The brain stem CPG will be analyzed here in terms of its location, the firing behavior of the neurons, the patterns of connectivity and the neurotransmitters involved. The regulation of the central program by central or peripheral inputs and some tentative mechanisms possibly underlying CPG activity will also be examined. Although a detailed analysis of the swallowing motor pattern is beyond the scope of this review, the various motor patterns correlated with swallowing, which are relevant to the interpretation of central nervous mechanisms, will be briefly described before the neurophysiological analyses are discussed.

II. MOTOR ACTIVITY

A. The Sequential Swallowing Pattern: Oropharyngeal Deglutition and Primary Peristalsis of the Esophagus

The motor activity of the two stages of swallowing shows different features. The oropharyngeal stage of the basic or fundamental swallowing is a complex, stereotyped sequence of excitatory and inhibitory events (87). It involves a set of muscles that always participate in this fundamental motor pattern, and therefore, these muscles have been termed obligate muscles (87, 90). In addition to the obligate muscles, other muscles, such as extrinsic tongue muscles, facial muscles, lip muscles, and levator mandible muscles, may or may not participate in swallowing, depending on either the species or the swallowing conditions, and therefore constitute facultative deglutition muscles (90).

The onset of the oropharyngeal stage of swallowing starts in most species with the contraction of the mylohyoid muscle, which can be taken to be the first muscle to become active in swallowing (87, 88). At the same time or after a very short delay of 30–40 ms, a contraction also begins in the anterior digastric and internal pterygoid muscles, concurrently with that occurring in the geniohyoid, stylohyoid, styloglossus, posterior tongue, superior constrictor, palatoglossus, and palatopharyngeus. All these muscles constitute, along with the mylohyoid, the “leading complex” that invariably initiates the act of swallowing (Fig. 1A) (88). The sequence continues with a pattern of excitation and inhibition in pharyngeal and laryngeal muscles. The middle and inferior pharyngeal constrictors fire in an overlapping sequence, and the inhibitory phenomena are particularly striking in laryngeal muscles such as the posterior crycoarytenoid, which becomes silent for several hundred of milliseconds (87). The oropharyngeal phase ends when the wave of contraction reaches the upper esophageal sphincter. At rest, the sphincter is closed by the tonic contraction of the cricopharyngeal muscle, which plays the main role in the sphincteric function (8, 9, 13, 49, 129, 301). Inhibition of the tonic contraction, resulting in the relaxation and opening of the sphincter, starts at the onset of swallowing and lasts until the cricopharyngeal muscle becomes active and propels the bolus into the esophageal body (Fig. 1, A and B) (110, 111, 164, 226).

The duration of the whole oropharyngeal sequence is in the range of 0.6–1 s and remarkably constant in all the mammals studied, including humans (87, 110). The electromyographic activity in each individual muscle consists of a phasic discharge, in the form of a burst of spikes, which ranges in general between 200 and 600 ms, depending on the muscle (88, 140, 171). The wave of contraction travels down the oro- and hypopharynx at a speed of ~10–20 cm/s before reaching the upper esophageal sphincter. This wave of contraction develops a force with a peak amplitude in the range of 100 mmHg in the oropharynx, reaching up to 200 mmHg in the human hypopharynx (Fig. 1B) (110, 353). When initiated by stimulation of the SLN, swallowing does not start immediately but occurs after a variable delay. Depending on the species, this delay ranges from 100 ms in sheep to 40–60 ms in rats (Fig. 4) (149, 152, 174). The presence of this delay suggests that the central nervous system comes into play during this period and participates in organizing the swallowing motor pattern.

In addition to the firing activity, when background activity is present in the muscles, it is abruptly inhibited
with the onset of firing in the leading complex, and this inhibition is maintained until the actual swallowing contraction begins (Fig. 1A) (87, 88, 140, 171). Inhibition can also be detected in muscles of the leading complex just before they contract during swallowing (88). A strong inhibition of the background activity is also observed after the cessation of the firing activity. Therefore, the oropharyngeal stage comprises an extraordinary sequence of inhibition and activation in pairs of muscles, which have to be synchronized during the motor sequence (70, 87). It is particularly striking that this complex motor sequence constitutes an "all or none" motor activity, just like simpler reflexes. In other words, once it has been initiated, the sequence invariably reaches the pharyngo-esophageal junction (87, 231).

In comparison with the extraordinary complexity of the oropharyngeal phase, the esophageal phase of swallowing is quite simple. It consists of a peristaltic wave of contraction, which propagates down the esophagus, enabling the alimentary bolus to be transported from the pharynx to the stomach (111, 128, 129, 142, 164). At rest, the esophagus is electromyographically silent, i.e., there is no tonic or rhythmic activity. The peristaltic contraction moves from the proximal to the distal part of the esophagus at a speed that may show a fairly high degree of variability, depending on the species and the nature of the muscles, i.e., on whether an esophagus is composed of striated muscle alone or of both striated and smooth muscle. For example, the whole esophageal phase can last less than 2 s in anesthetized sheep and exceed 10 s in conscious humans (79, 87, 110, 149, 152, 353). Among all the species combined, the mean velocity of the peristaltic wave can be evaluated at between 2 and 4 cm/s, a value conspicuously lower than that obtained in the case of the oropharyngeal sequence. The amplitude of the peristaltic wave is more variable than in the oropharynx. It may be lower, ranging between 35 and 70 mmHg, but may reach upper values of 180–200 mmHg (Fig. 1B) (110, 111, 275, 353). The duration of the contraction at the segmental level is longer than that observed in the oropharyngeal muscles. It generally exceeds 1 s and can reach values of up to 4 s, depending on the level of the esophagus and the nature of the muscle (129, 336). The esophageal phase ends when the contraction wave reaches the lower esoph-
ageal sphincter and propels the bolus down into the stomach. At rest, the lower sphincter is the site of a high pressure zone that prevents the reflux of food from the stomach. The factors contributing to the basal sphincter tone are multiple (78, 79, 110, 111, 164). In most species, the tonic contraction is mediated by a tonic depolarization of the smooth muscle fibers, without any action potentials (111, 280). During swallowing, the sphincteric tone is inhibited at the beginning of a swallow or after a short delay. That is to say that this tone is inhibited during the whole swallowing sequence until a phasic contraction of the sphincter occurs, as at the upper sphincteric level (Fig. 1, A and B) (79, 110, 164).

Because there is no basal tone in the esophagus at rest, esophageal peristalsis has been thought of as just a sequence of excitatory events corresponding to the propagation of the contraction wave. However, several lines of evidence suggest that the esophageal peristaltic contraction, like the oropharyngeal sequence, not only consists of a single sequential contraction but that this contraction is preceded by an inhibitory input, which has been called deglutitive inhibition. The lower sphincter relaxation is a component of the deglutitive inhibition. At the other levels of the esophagus, the inhibition is not usually detectable in the absence of basal tone, but becomes clearly visible during repetitive swallowing (79, 110, 353). By artificially setting up a high pressure zone in the human esophagus by inserting an intraluminal balloon and inflating it to a critical level, Sifrim et al. (303, 304) have also observed the occurrence of a deglutitive-induced inhibitory influence before the esophageal contraction. This inhibition begins simultaneously at various levels of the esophagus but lasts progressively longer as it reaches the more distal segments. In addition, in vivo recordings on the opossum smooth muscle have shown that even without any pressure changes in the esophageal body, a membrane hyperpolarization of variable amplitude and duration precedes the muscular contraction (273, 311). Therefore, it seems very likely that, as in the oropharynx, the sequential pattern occurring in the esophagus is a sequence of inhibitory and excitatory events.

Upon comparing the duration of the contractions, the velocity of the contraction waves and the pressures developed, it becomes quite obvious that the esophageal phase has quite different characteristics from the oropharyngeal phase. In addition, unlike the oropharyngeal phase, esophageal peristalsis shows some degree of variability. The contraction wave can stop before reaching the sphincter, even in awake animals (9, 86, 149, 152, 218, 302, 353). Esophageal peristalsis is therefore not an all or none sequence, which suggests that some differences may exist between the central mechanisms involved in the esophageal versus the oropharyngeal sequence.

B. Rhythmic Swallowing Movements

Rhythmic swallowing behavior can occur during physiological activities such as drinking, which involves a train of closely spaced swallows. It has been reported that depending on the amount of liquid being drunk, several successive swallows occur, numbering up to 100 in horses (87). Under experimental conditions, the best way of inducing rhythmic swallowing is to apply long-lasting repetitive stimulation to the SLN (Fig. 3) (86, 149, 225, 279). Under repetitive stimulation of the SLN, at 20–30 Hz, swallowing rates of 1–2/s can be readily induced in species such as rats and sheep during short periods of time (4–10 s) (149, 152, 174). Even during very long-lasting stimulation, the rhythmic pattern can continue, although obviously with a lower frequency. Under urethane anesthesia for example, a dog can swallow repetitively for 1 h at a rate of 0.4 Hz (87). In fact, as long as there is a bolus to swallow, or at least saliva, it is possible to observe sustained swallowing at a rapid rate with only slight signs of fatigue.

When swallows occur at a fast rate, the motor pattern consists of a series of complete oropharyngeal phases, whereas the esophagus remains quiescent and the lower esophageal sphincter is relaxed. A normal peristaltic contraction wave does not occur until after the last swallow in the series (Fig. 3A) (12, 221, 350). That is to say that during repetitive swallowing, the so-called deglutitive inhibition continuously blocks the esophageal activity. When the rate of the oropharyngeal swallowing is slow, the esophageal peristalsis is initiated but then interrupted or modified depending on when the subsequent swallow occurs during the peristalsis and on the nature of the muscle (striated or smooth) (350). When striated muscle only is involved, a second swallow initiated during the primary peristalsis results in the immediate and complete inhibition of the contractile activity induced by the first swallow, and the first wave progresses no further (Fig. 3A) (129, 152, 277, 279). In the species with smooth muscle distal esophagus, the pattern may be different, probably due to intricate interactions between central and peripheral effects. When the first swallowing wave has reached the smooth muscle segment of the esophagus, the peristaltic wave is not interrupted at this segment by the next swallow, but can proceed distally, although it decreases gradually in amplitude until it disappears (350). In these species, a previous swallow or the presence of a swallowing wave within the esophagus can dramatically alter the nature of the subsequent esophageal wave by decreasing its amplitude, modifying its velocity, and sometimes rendering it nonperistaltic (350). Whatever the case may be, depending on the duration of the whole swallowing sequence and the frequency of the rhythmic activities, the rhythmic swallowing motor pattern mainly
involves the oropharyngeal phase, which suggests that an oscillatory activity may take place at the central level.

C. Motility of the Esophagus: Secondary and Autonomic Peristalsis

Part of the swallowing sequence, namely, an esophageal peristalsis, can also be induced in the absence of the oropharyngeal phase of swallowing and is called secondary peristalsis (219). Secondary peristalsis occurs in response to stimulation of sensory receptors in the esophagus. For example, the transient esophageal distension induced by rapidly inflating an intraluminal balloon can induce peristaltic contractions in the esophagus. This may correspond to the distensions produced when the esophageal content is not completely cleared by the first swallow, or when reflux of the gastric contents occurs into the esophagus. Secondary peristalsis may be initiated at the level of either the striated or the smooth muscle. The wave of contraction usually begins at the level of the distension or just above it (79, 110, 111, 280, 353).

Once initiated, the secondary peristaltic wave progresses distally through the esophagus, like the primary peristalsis (101, 129, 280). The amplitude and velocity of the peristaltic contractions induced by esophageal distension are similar to those observed during primary peristalsis. Secondary peristalsis can also be either complete or interrupted at a variable distance from the level at which it has been initiated. It should be noted, however, that whether or not a transient distension suffices to induce secondary peristalsis in the smooth muscle esophagus, the presence of a bolus may be required for the peristaltic wave to be propagated down the whole esophagus in species with a striated muscle esophagus (147, 149, 152, 276, 277). Secondary peristalsis also involves a sequence of inhibitory and excitatory events, as shown by the relaxation of the lower esophageal sphincter, which begins when the wave of contraction is initiated and lasts until the contraction reaches the sphincteric level (111, 263).

Finally, a peristaltic contraction can still be obtained in the smooth muscle segment of the esophagus in the absence of any extrinsic innervation. This peristaltic contraction is called tertiary or autonomic peristalsis because of the peripheral nature of the underlying mechanisms (60, 78, 79, 111, 280).

D. Other Types of Movements

Some of the muscles that are involved in the motor performance of swallowing also participate in several other types of motor behavior. These motor activities can be subdivided into simple motor events, called elementary reflexes, and more complex motor patterns such as mastication, respiration, speech, and several protective reflexes.

1. Elementary reflexes

Electrical or natural stimulation of either the oropharynxo-laryngeal area or the esophagus can evoke in the same musculature a variety of simple reflexes. These responses can also be elicited by stimulating central end of nerves which innervate these regions such as the trigeminal, lingual, glossopharyngeal, vagal, superior laryngeal, and recurrent laryngeal nerves (Fig. 4A) (87, 88, 90, 212, 279). The reflex response evoked by nerve stimulation is generally ipsilateral, or at least it is much stronger ipsilaterally. The motor responses evoked consist of short electromyographic activities, lasting for ~10 ms. The latency of the responses is also short, since the minimal latency is in the range of 6–10 ms, depending on the muscle and the afferent fibers involved (87, 90). The reflex pathway may be monosynaptic, as in the case of the jaw closing muscles, but most of these elementary reflexes are mediated via oligosynaptic circuits (90).

With regard to the swallowing muscles, the elementary reflexes evoked by stimulating the SLN can also involve many nonlaryngeal muscles such as the geniohyoid, palatopharyngeus, and thyrohyoid muscles, the pharyngeal constrictors, and muscles of the tongue and upper cervical esophagus (87, 90, 279). All these muscles are obligate swallowing muscles, which means that the SLN strongly influences the motoneurons that innervate these muscles. The elementary reflex responses interact with the more complex swallowing behavior. The latter exerts the most powerful control on the motoneuronal pool and to a large degree overrides the effects of the elementary reflexes (Fig. 4A) (88). These findings indicate that the circuitry involved in the elementary reflexes, or at least part of this circuitry, also participates in swallowing.

2. Involvement of swallowing muscles in other motor behaviors

Swallowing muscles in the oropharynx and larynx are also involved in several other integrated behaviors, such as the activities involved in the preparatory oral phases of ingestive behavior, i.e., lapping, licking, sucking, and mastication (90, 296, 326, 368). Muscles innervated by the trigeminal motor nucleus, such as the mylohyoid, anterior digastric, and lateral pterygoid, are involved in jaw opening and chewing, during which they have a typical rhythmic activity (90, 215, 322, 326, 368). Muscles innervated by the facial motor nucleus, such as the stylohyoid and posterior digastric muscles, intervene in jaw movements (90). Tongue muscles controlled by the hypoglossal nucleus, such as the genioglossus and styloglossus, which are involved in protrusion and retraction of the tongue, respectively, are also among those mainly...
involved in all oral activities such as chewing, licking, and sucking (83, 200, 296, 326, 342).

Several swallowing muscles in the mouth, pharynx, and larynx exhibit either an inspiratory or an expiratory activity. This respiratory activity in oro-pharyngo-laryngeal muscles ensures the patency of the upper airway and regulates the airflow during the respiratory cycle (19, 81, 143, 352). Adductor muscles of the larynx are active during the expiratory phase of the respiratory cycle and regulate the rate of airflow during expiration, whereas abductor muscles become active during inspiration, thus ensuring airway patency (19, 87). In addition to participating in swallowing and respiration, laryngeal muscles obviously participate strongly in the various types of phonation (105, 239, 241, 369). Intrinsic and extrinsic tongue muscles, such as the genioglossus, also contribute to the respiratory activity and may be active during either inspiration or expiration (200, 201, 372). The tongue tonus, in particular, is important in the maintenance of the appropriate airway aperture. Pharyngeal muscles can also be active during one or the other phase of the respiratory cycle (112, 299, 352). With regard to the relationships between swallowing and respiration, in early asphyxia, most or all of the muscles active in deglutition are recruited and participate in the respiratory effort. In these cases, the muscles are active only in respiration (88). Under these conditions, the respiratory drive therefore overrides the swallowing drive.

Emesis is a complex sequential and coordinated motor activity, which involves some of the muscles which participate in swallowing (187, 188). During emesis, an opening of both the lower and upper esophageal sphincters occurs and antiperistaltic contractions of the esophagus are generated, particularly in its cervical portion (187–189). Several oropharyngeal muscles also contract, especially the laryngeal muscles acting as glottis closers, pharyngeal dilator muscles, geniohyoid, genioglossus, and digastric muscles (113, 347). Most of these muscles are also active during retching, which may precede the expulsion phase of the emetic reflex. Ruminations are a reflex motor sequence whereby animals such as cow and sheep regurgitate food from the stomach back to the mouth, where it is chewed again and then reswallowed (52, 91, 110, 276, 277, 308). During ruminations, the esophageal sphincters relax and an antiperistaltic wave occurs concomitantly, in this case involving the whole esophagus. Swallowing muscles are also activated during activities such as coughing, belching, eructation, regurgitation, and several other rather particular types of behavior (110).

This brief survey shows the extraordinary diversity of the behavior in which the muscles participating in swallowing are also involved. These muscles can participate in reverse motor activities, such as rumination or vomiting compared with deglutition, or even in such antagonistic pairs of activities as respiration and swallowing, speaking and swallowing, or jaw opening and swallowing. They constitute an example subscribing to the general rule whereby motoneurons serve as a common final pathway.

III. THE NEURONAL NETWORK GENERATING SWALLOWING

A. Localization and Functional Significance of the Swallowing Center Neurons

Primary lesion experiments as well as electrophysiological and more recent pharmacological and neuroanatomical experiments have generally yielded fairly concordant results as regards the swallowing CPG (24, 51, 87, 156, 226, 280). It was on the basis of microelectrode recordings, however, that the swallowing-related neurons were identified and the structures where they are located were mainly established, and a general picture of the organization and functional principles of the swallowing CPG was built up (154, 156, 161). Most of the data obtained in this connection were obtained in experiments performed on anesthetized or decerebrate animals. In addition, under these experimental conditions, swallowing was frequently reflexively elicited by applying electrical stimulation to the SLN, in many cases in paralyzed animals, thus resulting in a fictive swallowing pattern. Therefore, these results relate more to the stereotyped basic swallowing movement than to the physiological motor activity involved in alimentary and drinking behavior, which shows greater variability and a higher degree of complexity (87, 90, 164).

As regards the swallowing CPG, microelectrode data have been obtained on several species, such as the cat, dog, monkey, rat, and sheep (59, 149, 174, 246, 255, 314, 345), but the most extensive studies have been carried out on anesthetized sheep (5, 46, 47, 61, 62, 149, 151, 152, 159, 160). In addition, most of these results have been obtained by performing extracellular recordings. Only recently have intracellular recordings been successfully obtained on swallowing neurons, focusing mainly on the activity of motoneurons (337, 376, 377), whereas few intracellular recordings have been carried out so far on swallowing interneurons (106). When recorded extracellularly, the vast majority of the swallowing-related neurons, which will be referred to hereafter as swallowing neurons, are phasic neurons that are usually silent but produce a burst of spikes, which has been called “swallowing activity” (Fig. 2) (149), the timing of which is correlated with the swallowing motor activity. Spontaneously active neurons have also been found to participate in swallowing. Depending on the neuron, they can exhibit either a temporary increase in their discharge frequency or a phasic
inhibition of their spontaneous discharge during swallowing (Fig. 2A) (149, 152, 174, 345). Depending on the temporal relationship between their activity and the onset of swallowing, these swallowing neurons have been classified into three categories: “early” or oropharyngeal neurons, firing before or during the oropharyngeal phase of swallowing, and “late” and “very late” esophageal neurons, discharging during the esophageal peristalsis, that is to say during the cervical or thoracic esophageal contractions, respectively (Fig. 2) (149, 152). In addition to firing during the motor swallowing sequence, the swallowing neurons can also be activated by a local distension of the region of the alimentary canal which contracts in phase with the neuronal firing (Fig. 6A1). The swallowing neurons can furthermore be subdivided into motoneurons and interneurons.

1. Motoneurons

Motoneurons active in swallowing have been identified using criteria such as whether they are antidromically activated in response to stimulation of motor nerves, their discharge frequency, and the location of the recording electrode site. However, no very extensive electrophysiological studies have been carried out so far on swallowing motoneurons. These motoneurons are localized within the trigeminal (V), facial (VII), and hypoglossal (XII) motor nuclei, the nucleus ambiguus (IX, X), the dorsal motor nucleus of the vagus (X), and at the cervical spinal level between C1 and C3 (51, 87, 90, 156, 226). However, depending on which muscles are innervated by these motor nuclei and on the size of the population of motoneurons actually involved in swallowing, these motor nuclei do not all participate to an equal extent in swallowing, at least during the basic pattern.

V and VII motor nuclei do not deal mainly with swallowing (87, 90). They are most strongly involved in several other orofacial activities such as jaw reflexes, mastication, licking, and sucking (90, 326, 368). Lesion experiments have shown for example that abolishing the V motor nuclei does not affect the swallowing sequence (87, 89, 152). Trigeminal motoneurons mainly involved in swallowing innervate the mylohyoid, anterior digastric, lateral pterygoid, and tensor veli palatini (87). Within the VII motor nucleus, motoneurons greatly involved in swallowing control the posterior digastric and stylohyoid (87). Other muscles innervated by these two motor nuclei, such as the medial pterygoid, temporal, and masseter are more facultative swallowing muscles (70, 90). In fact, the main motor nuclei involved in swallowing are the XII motor nucleus and the nucleus ambiguus. Most, if not all, of the motoneurons within these nuclei, which innervate the intrinsic and extrinsic muscles of the tongue, such as the genioglossus, geniohyoid, styloglossus and hyoglossus,
and the pharynx, larynx, and esophagus, participate in swallowing (87, 226).

Data have shown the existence of a mototopic pattern of organization within the motor nuclei. This pattern of organization is based on a series of dorsoventral and mediolateral subdivisions in V, VII, and XII motor nuclei (341), i.e., the mylohyoid and anterior digastric motoneurons are situated in the ventromedial region of V motor nucleus, and tongue protrudor motoneurons are located in XII ventrolateral nucleus, whereas the tongue retractors are to be found more dorsolaterally (102, 181, 182, 196, 207, 234, 256, 344). The mototopic organization of the nucleus ambiguus corresponds to the well-known rostrocaudal pattern of organization of the motoneurons innervating the esophagus, pharynx, and larynx (28, 191–193), where the esophageal motoneurons are localized in the rostral compact formation of the nucleus, the pharyngeal and soft palate motoneurons in the intermediate semicompact formation, and most of the laryngeal motoneurons in the caudal loose formation of the nucleus. This scheme of organization results in the sequential firing of nucleus ambiguus motoneurons during swallowing. However, the various pools of motor nuclei are not involved in any ordered sequence during swallowing, since the contraction of muscles in the leading complex involves motoneurons in V, VII, and XII motor nuclei and the nucleus ambiguus (88).

With regard to the innervation of the smooth muscle esophagus, the majority of the preganglionic neurons are located within the X motor nucleus. It has been reported that experimental lesion of this nucleus in the cat impairs the motility of the smooth muscle esophagus (131). Moreover, after injecting tracer into the cat esophagus and lower esophageal sphincter, most of the labeled cells have been observed in the X motor nucleus, although some neurons have also been identified in the nucleus ambiguous (66, 247). Unlike the striated motoneurons, which are located compactly in a single region, the preganglionic esophageal neurons consist of two separate groups: the one located in the rostral part of the X motor nucleus and the other in its caudal portion (66, 284).

Extracellular recordings have shown that within V and XII motor nuclei and the nucleus ambiguous (46, 47, 149, 151, 152, 174), the oropharyngeal motoneurons, which are generally silent at rest, exhibit during swallowing a short burst of low-frequency (40–50 Hz) spikes with a duration in the 50- to 200-ms range and considerable overlapping between the discharge of the various neurons. The bursting discharge can either precede the beginning of swallowing by a few milliseconds or lag between 0 and 200 ms behind the onset of the sequence. The firing behavior of esophageal motoneurons is somewhat different (152, 183, 377). However, the results published to date on these motoneurons are mainly restricted to sheep. The bursting discharge has a longer duration (up to 800 ms) and a very low frequency (10–20 Hz) and lags from 200–300 ms to 2 s behind the onset of swallowing. Therefore, the swallowing activity has a longer duration and a lower frequency in the esophageal than in the oropharyngeal motoneurons; the later the neuron becomes active during swallowing, the longer it will fire and the lower its discharge frequency will be (see Table 1).

In addition to the burst firing that occurs in motoneurons during swallowing, they can exhibit a short-latency (7–12 ms) synaptic activation, which is also called initial activity. This initial activity consists of one spike elicited in oropharyngeal or esophageal neurons by stimulating the afferent fibers present in the SLN or the vagus nerve, respectively (46, 47, 149, 151, 152, 174, 317). This initial activity has been observed only in response to ipsilateral

<table>
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<th>TABLE 1. Comparison of discharge characteristics and localization between oropharyngeal and esophageal medullary neurons</th>
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<tr>
<td><strong>Oropharyngeal Neurons</strong></td>
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<td>Interneurons</td>
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<td>Burst duration, ms</td>
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For further explanations and references, see text (sects. iii and iv, A and B). nA, nucleus ambiguous; NTS, nucleus tractus solitarii.
stimulation applied to afferent fibers. Several pulses are generally required to initiate the spike, the latency of which is variable and suggests the existence of a polysynaptic pathway.

No central recordings have been performed so far on the activity of the preganglionic vagal neurons that innervate the smooth muscle esophagus. The data available on this subject were obtained in cross-innervation experiments and by directly recording the activity of vagal fibers (109, 281). They show that these neurons operate an ordered sequence during swallowing, which suggests that a central control may be at work even in the case of the smooth muscle esophagus. The burst firing of the preganglionic vagal neurons driving the smooth muscle esophagus has a long duration, in the range of 1 s, and a very low frequency, i.e., 3–8 Hz (109, 281). Recordings of the vagal efferent fibers innervating the opossum esophagus and the dog lower esophageal sphincter, both of which are composed of smooth muscle, indicate that both the vagal excitatory and inhibitory pathways are involved in swallowing (109, 233). These results therefore show that the CPG exerts both an excitatory and an inhibitory drive on the smooth musculature.

Recent intracellular recordings on hypoglossal and nucleus ambiguous motoneurons (337, 376, 377) have shown that, during swallowing, the firing of motoneurons was superimposed on a bell-shaped membrane depolarization. This simple bell-shaped depolarization of the membrane potential is not the only event that has been found to accompany the firing of these motoneurons. In some cases, complex depolarizing-hyperpolarizing or hyperpolarizing-depolarizing waves of membrane potential are evoked in motoneurons during swallowing (Fig. 6D). This indicates that in addition to an excitatory drive, these motoneurons may also receive inhibitory inputs or have complex intrinsic properties that are activated by the swallowing drive.

2. Interneurons

Extensive microelectrode recordings, first performed on sheep (5, 61, 62, 149, 151, 152, 159) and subsequently on the rat, dog, cat, and monkey (59, 94, 174, 190, 202, 246, 345), have shown that the swallowing neurons are located in two main brain stem areas: 1) in the dorsal medulla within the nucleus tractus solitarii (NTS) and in the adjacent reticular formation, where they form the dorsal swallowing group (DSG), and 2) in the ventrolateral medulla, just above the nucleus ambiguus, where they form the ventral swallowing group (VSG). Swallowing neurons are therefore located in the same medullary sites where are situated neurons that belong to CPGs involved in respiration and cardiovascular regulation (21, 73, 99, 163). In addition, other swallowing-related neurons have been identified within or very close to the motor nuclei and in the pons, at the level of the sensory nucleus of the trigeminal nerve (46, 47, 152, 160, 174, 254).

The results of microelectrode recording studies have not corroborated the lesion and anatomical data, suggesting that the swallowing CPG might be located rostrally in the medial reticular formation. Doty et al. (89) postulated that the interneuronal network that organizes swallowing might be located within the medial reticular formation, between the posterior pole of the facial nucleus and the rostral pole of the inferior olive. This assumption was based on lesion experiments performed on various species (e.g., on cats, dogs, and monkeys), which severely affected the motor pattern. The anatomical results obtained on the cat by Holstege et al. (137) have suggested that part of the “swallowing center” might be present in the pontine tegmental area just dorsomedial to the superior olivary complex. In fact, the latter data were obtained with tracing techniques, which can be used to demonstrate connections between neurons but not to identify the function of any such connections. Moreover, there is no direct evidence that any swallowing-related neurons exist within these regions; their possible role in swallowing still remains to be determined.

A) DORSAL SWALLOWING GROUP: THE INTERNEURONAL POPULATION IN THE NTS. Within the NTS, there exist neurons that fire during either the oropharyngeal or the esophageal phase of swallowing (149, 152). These neurons exhibit a typical sequential firing pattern that parallels the sequential motor pattern typical of deglutition (Fig. 2). When rhythmic oropharyngeal phases of swallowing are elicited, NTS neurons involved in the oropharyngeal sequence produce rhythmic bursting discharges that are closely linked to the motor pattern (Fig. 3). Because these neurons are still active during fictive swallowing elicited in paralyzed animals, their bursting discharge cannot be due to peripheral afferent inputs generated by the muscular contraction and actually correspond to a central swallowing activity (149, 152, 174). These results have amply confirmed that swallowing is a centrally patterned motor activity, as suggested in the pioneer study by Meltzer (218), and demonstrate that NTS medullary neurons form part of the neuronal network that generates swallowing. In previous studies on the cat, Sumi (314) failed to detect any bursting activity in the NTS during fictive swallowing. However, recent studies have provided evidence that in the cat also, there exist NTS neurons involved in swallowing that have a centrally patterned activity (106, 345).

Most of the oropharyngeal neurons are active either just a few milliseconds before or during the oropharyngeal phase of swallowing. The firing pattern of these neurons is characterized by a short burst of spikes, with a duration in the range of 100–300 ms, a steady or an increasing-decreasing frequency with a mean value in the range of 100 Hz, and an instantaneous frequency that can...
Recent intracellular studies on cats have shown that the bursting activity of oropharyngeal NTS neurons is superimposed on a high-amplitude depolarizing wave, between 15 and 20 mV, which indicates that a strong central drive is exerted during swallowing (Fig. 3C) (106). As we saw above with the motoneurons, the firing behavior of the esophageal neurons differs from that of the oropharyngeal neurons. The duration of the bursts of spikes is longer (between 200 ms and 1 s), and the firing frequency is much lower, since it does not exceed 40 Hz in the case of the late neurons and is as low as 10–20 Hz in that of the very late neurons (Fig. 2B). At the level of the interneurons, one can also observe an increase in the duration of the discharge and a decrease in the firing frequency when the neuron is active later during swallowing (Table 1). No central recordings have been performed so far on esophageal neurons in species with a smooth muscle esophagus.

When stimulation is applied to afferent fibers, both types (oropharyngeal and esophageal) of interneurons produce a synaptic response (initial activity) in the form of a single spike. This initial activity can be elicited by stimulating the ipsilateral SLN in all the oropharyngeal NTS neurons and in the late esophageal neurons, the firing behavior of which is linked to the activity of the upper cervical esophagus (Figs. 4B and 6A). In the very late esophageal neurons, an initial activity can be elicited by stimulating the cervical vagus (149, 152). The synaptic response may occur with a very short, stable latency of 1–2 ms, indicating that, at least some, of these neurons are monosynaptically connected to afferent fibers (149, 152, 255, 294). In these types of neurons, the synaptic response
and the burst firing activity are clearly separated by an interval of variable length, depending on the order at which the neuron is recruited in the sequence (Figs. 4B and 6A).

Among NTS oropharyngeal neurons, some exhibit a particular pattern of bursting activity starting before the onset of the swallowing motor sequence. Unlike those neurons, where the swallowing burst occurs with a phase lag after stimulation and only when a swallow is initiated, these neurons exhibit a continuous discharge in response to the stimulus. This discharge, called “preswallowing activity,” starts long before the beginning of the muscular contraction. It decreases and stops quite rapidly when no swallowing occurs, but continues and increases, turning into a swallowing activity, when swallowing is initiated (Figs. 2 and 4, C and D). This pattern of discharge suggests that these neurons are involved in the initiation of swallowing, and it has been postulated that they may constitute the trigger neurons in deglutition (149, 152).

As regards the location of NTS swallowing neurons, most of the relevant data were obtained before the cytoarchitectonic subdivisions of the nucleus were established on the basis of anatomical studies (1, 17, 157, 167). Therefore, their location has not been specified in relation to these subdivisions. However, in all the species studied, it has emerged that the oropharyngeal neurons are situated rostrocaudally at the level of the intermediate-subpostremal portion of the NTS (17), within the medial part of the lateral NTS which overlaps the interstitial, intermediate, ventral, and, to some extent, the ventrolateral sub-
divisions of the nucleus (149, 152, 161, 174). The esophageal neurons, which to date have been clearly identified only in sheep, are also situated at the level of the intermediasubpostremal part of the nucleus, between the tractus solitarius and the X motor nucleus (149, 152), a region which may correspond to the centralis subdivision of the NTS in the rat (1, 202). Interestingly, anatomical results have shown that both laryngeal and pharyngeal afferent fibers project mainly to the interstitial subdivision of the NTS in all the species studied and that the esophageal afferent fibers end within the NTS subnucleus centralis, at least in the rat (1, 238). Therefore, within the NTS, there are these two subnuclei that are mainly concerned with swallowing (see Table 1).

b) VSG. In the ventrolateral medulla above the nucleus ambiguus, there also exists a large population of oropharyngeal swallowing neurons (59, 94, 149, 151, 152, 174, 252, 345). These neurons have been identified as interneurons on the basis of criteria, such as the lack of antidromic activation by vagus nerve stimulation and a high discharge frequency. In addition, several neurons in this region fire during the leading phase of swallowing, before most of the motoneurons in the nucleus ambiguous become active. The burst firing behavior of the VSG neurons is very similar to that of the DSG neurons in terms of the sequential firing pattern, in which there is considerable overlap, discharge duration, and frequency. This population has, however, a lower instantaneous discharge frequency, which never reaches the higher instantaneous values (400 Hz) observed in the DSG neurons (149, 152, 174). The main difference lies in the synaptic response to stimulation of the SLN. The initial activity is not readily triggered in these VSG neurons with a single pulse, and several pulses are generally required to initiate the response. Moreover, the fact that the latency is visibly longer (between 7 and 12 ms) and shows some degree of variability suggests the existence of a polysynaptic connection between the afferent fibers and the neurons (149, 174, 255; see Table 1).

The existence of a large population of esophageal interneurons in the ventrolateral medulla is less clear. Bursting discharges in phase with esophageal peristalsis have been recorded in the medullary region above the nucleus ambiguus (152). However, in the case of esophageal neurons, applying stimulation to the vagus nerve systematically induces an antidromic field potential. Without any intracellular evidence, it is therefore not possible in the case of esophageal neurons to clearly distinguish between motoneurons and actual interneurons (151, 152).

Whatever the case may be, swallowing neurons within the ventrolateral medulla are still active during fictive swallowing. Their bursting activity is therefore actually a central discharge, and these neurons, like those in the NTS, belong to the neuronal network that generates swallowing.

c) INTERNEURONS IN THE MOTONEURONAL POOLS. Apart from the VSG in the ventrolateral medulla, which probably plays an important role within the swallowing CPG (see sect. uB), swallowing interneurons have been identified within V and XII motor nuclei or in their close vicinity. These neurons produce a high-frequency discharge, and when tested by stimulating the motor nerves, they failed to respond antidromically (46, 47, 149, 174). These neurons may play the role of premotor neurons or be involved in the organization of the swallowing drive to the various motoneurons involved in swallowing within a single motor nucleus (254). Electrophysiological and neuroanatomical data also suggest that they might be involved in the bilateral coordination of the motoneuronal pools (5, 46, 47, 158, 235). The exact function of these neurons has not yet been elucidated, however, and further experiments will be required before this is possible.

d) PONTINE INTERNEURONS. In sheep, a population of neurons exhibiting burst firing in phase with the oropharyngeal stage of swallowing has been found to exist more rostrally in the pons, in a region extending rostrally to the exit of the facial nerve, above the V motor nucleus, at the level of the principal sensory trigeminal nucleus (160). These neurons, which are spontaneously active, present a swallowing activity in the form of a burst of spikes lasting some 40-380 ms, with a similar discharge frequency to that of the medullary interneurons, ranging between 60 and 340 Hz. In addition, they can be synaptically activated by applying stimulation to the ipsilateral SLN with a latency of 1.5-4 ms resembling that of the NTS neurons. However, there are two striking differences between these and the NTS neurons. In the pons, the swallowing burst always occurs after the beginning of swallowing and is abolished after motor paralysis of the animal. In addition, unlike NTS neurons, the pontine neurons are antidromically activated when stimulation is applied to the ventro-postero-medial nucleus of the thalamus (160). On the basis of these results, these pontine neurons have been classified as sensory relay neurons and are thought to be involved in providing information from the oropharyngeal receptors to the higher nervous centers. They therefore do not belong to the swallowing CPG.

B. Organization of the Neuronal Network

The detailed connections between the various groups of neurons within the swallowing CPG still remain to be mapped. However, the results of electrophysiological and anatomical experiments have provided some information about the organization of the DSG, VSG, and motoneurons (2, 152, 154, 156).

1. Connections between the various neuronal groups

The latency of the synaptic response (initial activity) is shorter among the neurons of the DSG than those of the
VSG. In the case of SLN stimulation, the latency is 1–4 ms in the DSG and 7–12 ms in the VSG (149, 151, 152, 159, 174, 255). A synaptic response can also be initiated in swallowing neurons by stimulating a specific cortical area, which induces swallowing (see sect. iv). Here again, the latency of the response is shorter in the NTS swallowing neurons (5–8 ms) than in the neurons in the ventrolateral medulla (10–16 ms) (152, 159). These results suggest that the neurons of the VSG are probably activated via neurons of the DSG. Indeed, regardless of which afferent pathway is stimulated, the initial response of the VSG neurons is abolished after lesion of the DSG (152, 159). Although no direct evidence is available at the single cell level that a connection of this kind exists between the DSG and VSG, connections between the NTS region and the ventrolateral reticular formation surrounding the nucleus ambiguus, where swallowing neurons are located, have been found to exist in several anatomical experiments (57, 69, 236, 249, 257, 258, 283, 288). Other anatomical results have shown that the ventrolateral medulla also projects to the NTS region (20, 126, 198, 282, 349). However, whether or not these possible reciprocal connections are involved in swallowing still remains to be established.

Electrophysiological experiments on sheep have shown that only the swallowing neurons within the VSG could be antidromically activated by stimulating the swallowing region of V motor nucleus, i.e., that region where swallowing motoneurons are located, while none of the neurons within the DSG exhibited any antidromic activation under the same conditions (5). These results indicate that the V motor nucleus is connected to only one of the medullary regions involved in swallowing, namely, the VSG. Similar results have also been obtained on the XII motor nucleus, the stimulation of which evoked an antidromic potential in swallowing neurons of the VSG (4). In addition, more recent electrophysiological studies on sheep and cats have established that within the VSG, the same identified swallowing neuron can project to more than one motor nucleus. It has been shown, for example, that the same neuron can project either to V and XII motor nuclei, or to the XII motor nucleus and the nucleus ambiguus (6, 94). Some data also suggest that the same neuron might project to V and XII motor nuclei and the nucleus ambiguus (94), which are all motor nuclei involved in swallowing. These electrophysiological data fit in well with those coming from anatomical studies. It has been shown that retrograde transport of peroxidase, injected under electrophysiological control into the region of the V motor nucleus where swallowing motoneurons are situated, resulted in labeling of neurons in the ventrolateral medulla. Control experiments with tritiated leucine, injected in the VSG region, show labeling in the ventromedial region of the V motor nucleus. In addition, these experiments showed that the ventrolateral medulla is also connected to the homologous contralateral medullary region and to VII, X, and XII motor nuclei, all of which are also involved in swallowing (158). The ventrolateral medulla, which contains swallowing neurons, is therefore connected to all the various groups of motoneurons involved in swallowing: this conclusion is in complete agreement with other anatomical data (138, 195, 343).

These results suggest that within the swallowing network, VSG neurons are activated via DSG neurons and that motoneurons are driven by neurons of the VSG (Fig. 5 and Table 2). If we therefore consider the swallowing CPG, there exist simple circuits linking together the afferent fibers, the DSG neurons, the VSG neurons, and the motoneurons. At each level obviously, i.e., within the NTS, the ventrolateral medulla and the motoneuronal pools, circuits more complex than a simple monosynaptic connection may exist. However, the trisynaptic circuits are probably basic elements in the functioning of the CPG. Such reflex loops are also probably basic in the elementary reflexes.

Recent results obtained with retrograde tract tracing techniques or by performing transneuronal labeling with pseudorabies virus indicate that a direct connection may exist between swallowing regions in the NTS and motoneurons in the nucleus ambiguus, at least in the rat (16, 18, 39, 125, 126). These studies show that NTS neurons, which are supposed to be esophageal neurons, since they are located in the subnucleus centralis where esophageal afferent fibers project, send axon terminals in the rostral compact formation of the nucleus ambiguus where esophageal motoneurons are situated. A direct connection between NTS esophageal neurons and esophageal motoneurons may exist, since the existence of an interneuronal pool of esophageal neurons has not been clearly demonstrated in the ventrolateral medulla. However, it seems unlikely that a direct connection of this kind exists in the case of oropharyngeal neurons (see sect. III). All the results available to date on functionally identified swallowing neurons have shown that motoneurons are driven by oropharyngeal neurons within the VSG. Therefore, it is puzzling that the oropharyngeal population of interneurons within the ventrolateral medulla, i.e., the VSG, was not determined in the anatomical studies. Recordings will have to be made on functionally identified neurons to be able to ascertain whether there exists a monosynaptic link between neurons in the DSG and motoneurons.

2. Role of the various interneuronal groups in the CPG

It has been established in several networks involved in basic motor behavior, such as locomotion, that within a given CPG all the neurons are not equal since some of them play a preeminent role (10, 117). As regards swallowing, data already obtained suggest that neurons in the
DSG are likely candidates to act as generator neurons in the initiation and organization of the sequential or rhythmic motor pattern (149, 152). The swallowing network in mammals therefore provides a unique example of neurons located within a primary sensory relay, i.e., the NTS, which nevertheless play the role of generator neurons. Several lines of evidence support the idea that NTS neurons play a leading role in swallowing. NTS neurons exhibit a sequential or rhythmic firing pattern that parallels the motor pattern (149, 152, 174). As this firing remains unaltered after complete motor paralysis, it is clear that it is actually a centrally generated premotor activity. Moreover, most of the neurons, if not all those which have a preswallowing activity, are located within the NTS (149, 152). In addition, systematic exploration of the brain stem with concentric bipolar electrodes to determine which central structures responded to stimulation by triggering deglutition have shown that the active points are situated only in the region of the solitary complex (50, 174, 225). It may be that deglutition results from the stimulation of afferent fibers belonging to the solitary tract. The wide dispersion of the active points suggests, however, that not only afferent fibers were stimulated but also neurons in or very close to the NTS. The assumption that NTS neurons may trigger swallowing was fully confirmed by more recent pharmacological experiments using fine microinjections of excitatory amino acids (EAA), which are thought to stimulate neuronal cell bodies and not passing fibers. It was established in these experiments that activating specific EAA receptors within the NTS elicit both the sequential and rhythmic swallowing patterns, whereas microinjections of the same drugs into the ventrolateral medulla failed to induce the swallowing motor pattern (124, 173, 178). Furthermore, electrolytic lesion of the NTS results in the abolition of not only the swallowing elicited by stimulating the SLN but also that elicited by stimulating the swallowing cortical area (152, 159). Finally, fine lesions performed on sheep in the NTS region, which contains neurons that control esophageal motility, abolished the esophageal phase of swallowing without

**Table 2. Connections between medullary swallowing neurons**

<table>
<thead>
<tr>
<th>Inputs to</th>
<th>Oropharyngeal VSG neurons</th>
<th>Oropharyngeal motoneurons</th>
<th>Esophageal DSG neurons</th>
<th>Esophageal motoneurons</th>
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<tbody>
<tr>
<td>Oropharyngeal DSG neurons</td>
<td>E (EAA)</td>
<td>?</td>
<td>I (GABA)/E (ACh)</td>
<td>I (?)</td>
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<td>Oropharyngeal VSG neurons</td>
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<td>Esophageal DSG neurons</td>
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<td></td>
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<td>E (EAA)</td>
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Connections have been established on the basis of electrophysiological and anatomical tract tracing techniques (see text and sects. III B and IV C for references). DSG, dorsal swallowing group; VSG, ventral swallowing group; E, excitatory connection; I, inhibitory connection; EAA, excitatory amino acids; ACh, acetylcholine.
affecting the oropharyngeal phase, which indicates that some of the neurons actually involved in the generation of esophageal motility had been destroyed within the NTS (150, 152).

As regards the swallowing neurons in the ventrolateral medulla, the results available are consistent with the view that during swallowing these neurons are driven by NTS neurons. As neurons of the VSG are connected to motoneurons, one of their functions probably consists of activating the motoneuronal pools during swallowing. The existence of neurons with collaterals to several pools of motoneurons also suggests that they may also participate in the coordination of the motoneuronal pools during swallowing (6, 94, 158). Within the swallowing CPG, the ventral swallowing neurons can therefore be said to act as switching neurons that distribute and coordinate the sequential or rhythmic drive generated in the dorsal group to the various pools of motoneurons involved in swallowing. It may well be that these neurons are also concerned in the coordination of the activity of motor nuclei (V, VII, IX, X, and XII) that are involved in several other types of motor behavior (see sect. ii).

This scheme of organization of the diverse groups of swallowing neurons does not mean that the connections between the dorsal group and the ventral group and those between the ventral group and the motoneurons include only excitatory connections. Indeed, recent results obtained in intracellular studies on swallowing motoneurons in XII motor nucleus and the nucleus ambiguus (337, 376, 377) have suggested that during the functioning of the network, both excitatory and inhibitory drives can be exerted along the anatomical pathways.

3. Synchronization of the two swallowing CPGs

In fact, the CPG for swallowing consists of two hemi-CPGs, each located on one side of the medulla (87). The existence of two hemi-CPGs was established by making longitudinal midline sections of the medulla. After this splitting, stimulation applied to the SLN on one side triggered a “unilateral swallowing,” i.e., a swallowing sequence involving only the ipsilateral oropharyngeal muscles, except for the middle and inferior pharyngeal constrictors in some species (87, 89, 150, 152). These results indicate that under physiological conditions, the two hemi-CPGs are tightly synchronized and organize the coordinated contraction of the bilateral muscles of the oropharyngeal region.

The mechanisms underlying the synchronization of the two hemi-CPGs are not known, and this matter has not yet been well documented. It is likely that the peripheral afferent fibers do not play an important role in the coordination of the CPGs, since lesion experiments have shown that splitting the medulla caudal to the obex, which interrupts the vagal afferent fibers crossing the midline through the solitary tract, does not affect swallowing, i.e., a bilateral deglutition still occurs in response to unilateral stimulation of the SLN (87). Moreover, microelectrode recordings have shown that the synaptic activity of swallowing neurons induced by stimulating the ipsilateral SLN is absent when it is the contralateral nerve that is stimulated (Fig. 4C). This finding indicates that the swallowing neurons receive a direct input only via the ipsilateral afferent fibers. There probably therefore exist connections between central neurons that play the key role in the coordination between the two hemi-CPGs. Anatomical connections mediated by fibers crossing the midline have been found to exist between the two medullary regions where swallowing neurons are located, i.e., the DSG and VSG (41, 158, 268).

The mechanisms involved in synchronization seem to include all the swallowing neurons, i.e., motoneurons as well as dorsal and ventral interneurons. Microelectrode recordings have shown that in each case, a particular swallowing neuron produces a swallowing bursting discharge in response to stimulation of the ipsilateral as well as to that of the contralateral afferent fibers, regardless of the type of swallowing neuron tested. This indicates that at each step in the network operation, the entire population of neurons within the NTS, the ventrolateral medulla, or the motoneuronal pools is active. Here again, however, the neuronal population within the NTS seems to play a particularly important role in the synchronization processes. The results of lesion experiments performed on the NTS esophageal neuronal population have shown that upon stimulating the ipsilateral SLN, only an oropharyngeal stage of swallowing is elicited, whereas upon stimulating the contralateral nerve, a complete process of glutation including the esophageal stage is initiated (150, 152). These results also suggest that, at each step, the appropriate coordination must take place between each NTS interneuronal populations for the drive to be distributed to the motoneurons.

These results suggest in addition that under ipsilateral stimulation conditions, the swallowing motor sequence is mainly generated in the ipsilateral hemi-CPG and that this CPG transfers the swallowing premotor signal to the contralateral CPG. This assumption is also supported by recordings showing the activity of neurons with preswallowing activity. These neurons displayed a clear-cut preswallowing discharge before the swallowing burst only when the ipsilateral SLN was stimulated. Upon stimulating the contralateral nerve, only the swallowing burst was recorded, which suggests that the preswallowing discharge occurs only in the corresponding neurons on the ipsilateral side and that only the swallowing drive is transmitted to the contralateral side (Fig. 4C) (152). Further experiments are required to elucidate the mechanisms underlying the synchronization of the two hemi-CPGs. The lesion and electrophysiological data available
indicate, however, that swallowing NTS neurons play a crucial role in these synchronization processes.

IV. ACTIVATION OF THE NEURONAL NETWORK AND MODULATION OF NETWORK ACTIVITY

A. Role of Sensory Inputs

Sensory inputs from peripheral areas play an essential part in inducing the whole swallowing motor sequence or parts of this motor sequence such as esophageal peristalsis (51, 87, 90, 156, 226). They play the prime role in reflex swallowing or secondary peristalsis, and they are also involved in voluntary swallowing. It is obviously very difficult to perform deglutition without having anything to swallow, and this is also the case when the oropharyngeal mucosa is anesthetized (87, 211, 267). Moreover, sensory inputs modulate the central network activity to adapt the forthcoming motor sequence to the information arising from peripheral receptors (155, 156).

It is generally assumed that the afferent fibers involved in the initiation of swallowing are those running within the maxillary branch of the trigeminal nerve, the glossopharyngeal nerve, and the vagus nerve, especially its SLN (87, 90, 224, 226). These nerves innervate peripheral areas such as the dorsum of the tongue, the epiglottis, pillars of the fauces, and walls of the posterior pharynx, the tactile or chemical stimulation of which induces swallowing (87, 90, 226, 231). Electrical stimulation of these nerves can also trigger swallowing. In fact, all the results obtained so far show that only stimulation applied to the SLN induces the highly specific swallowing pattern without any additional orofacial activity, i.e., “pure” swallowing, with a minimal latency. Interestingly, among the various patterns of stimulation used for this purpose and whatever the species under investigation, repetitive stimulation applied to the SLN at a frequency of around 30 Hz (in the 20- to 40-Hz range) acts like “magic” by producing pure swallowing at the lowest stimulus threshold (86, 87, 149, 174, 225, 279). Applying stimulation to the other afferent fibers is less effective, and the results obtained have been variable and often conflicting, depending on the species studied (61, 62, 86, 87, 255, 305, 306, 309, 310).

Frequently, the motor pattern was very different from that of pure swallowing and induced only at high stimulation intensities and after a long latency (87). It has been observed in a comparative study on sheep that IX nerve stimulation can facilitate swallowing but does not suffice to trigger the motor pattern, and stimulation applied to the maxillary branch of the V nerve cannot induce swallowing (61, 62). Therefore, although SLN afferent fibers are involved in triggering several other reflexes, they constitute the main afferent pathway involved in the initiation of swallowing. Within the SLN, there exist some fibers belonging to the groups Aα and Aδ which are mainly involved in swallowing (8, 230). In addition, it should be noted that esophageal afferent fibers running in the vagus can initiate part of the swallowing sequence, that is, esophageal peristalsis. These fibers are of the types A and C (63, 64, 96, 217, 293).

At the central level, all the afferent fibers involved in initiating or facilitating swallowing converge in the solitary tract and end in the NTS (67, 68, 167, 270, 338). The solitary tract and the NTS therefore constitute the main afferent central structures involved in swallowing, particularly the intermediate-subpostremal part of the solitary system, which receives vagal afferent fibers including those from the SLN (17, 87, 156). Indeed, stimulation applied to the solitary tract and its nucleus (NTS) can induce a very similar swallowing pattern to that obtained in response to SLN stimulation (50, 174, 225, 231, 244, 367). Furthermore, lesion of the solitary tract abolishes the swallowing induced by SLN stimulation (89, 152, 367).

Results obtained at the cellular level on swallowing-related neurons have supported the idea that SLN afferent fibers play a major role in the initiation of swallowing. In all the species studied, the results have shown that almost all the NTS swallowing neurons are synaptically activated by the SLN (149, 152, 174, 255, 345). In addition, it is very likely that in most cases, the swallowing neurons may receive a direct, i.e., monosynaptic, input from SLN afferent fibers (149, 174, 255). The arrangement of the SLN terminals in the interstitial NTS subnucleus, in the form of rosettes or glomeruli, also suggests that laryngeal afferent fibers may exert strong synaptic effects on postsynaptic elements (238). Electrophysiological results have indicated that most of the NTS oropharyngeal neurons can be activated also via IX afferent fibers (61, 255). It has been observed, in sheep and cats, that IX afferent fibers activated ~90% of the oropharyngeal neurons studied. However, the IX fibers seem to have less impact than SLN fibers on the swallowing neurons. Although the latency of the synaptic response to IX stimulation is in the same range as that recorded following SLN stimulation, it seems most likely that it is not monosynaptic, judging from the conduction distance and the variable latency (30, 61, 255, 294). These findings probably explain why the IX afferent fibers are relatively inefficient at initiating swallowing. It is still puzzling, however, that, at least in sheep, all the NTS neurons that display preswallowing activity have been found to be synaptically activated by both the SLN and the IX nerve (61). SLN afferent fibers can nevertheless induce a swallowing burst in these neurons upon receiving either a single stimulating pulse or repeated stimulation, whereas the IX can induce only preswallowing activity even when undergoing repetitive stimulation, which indicates that the activation of IX afferent fibers...
alone does not suffice for the swallowing threshold to be reached (Fig. 4D) (61).

Although the swallowing motor sequence is centrally organized, it can change as the result of peripheral afferent information (155). Studies on the swallowing motor sequence have strongly suggested that it is controlled by a peripheral feedback mechanism. It has been established that the amplitude and duration of the electromyographic activity of oropharyngeal muscles partly depends on the consistency of the bolus (140). The importance of sensory feedback for esophageal peristalsis was shown by experiments in which “wet” swallows (with various volumes of water) were found to be associated with a contraction wave with a slower speed and a greater amplitude and duration than “dry” swallows (85, 136). Direct evidence that sensory feedback intervenes during swallowing has been provided by afferent nerve recordings (9, 64, 98, 217). Studies on the activity of vagal sensory fibers in anesthetized cats and rats or conscious sheep have indicated that these fibers are strongly excited by the presence of a bolus or the passage of the peristaltic wave. All these results suggest that continuous sensory feedback may influence the neurons of the CPG and thus modulate the central program (95, 155). In fact, results obtained at the cellular level have shown that applying continuous stimulation to peripheral receptors by means of an inflated balloon can either induce a permanent activity in the neurons that are active during swallowing or modify the bursting activity occurring during swallowing (Fig. 6A). The early neurons can be activated by locally distending the pharyngeal cavity, whereas the late and very late neurons respond to local distension of the proximal and distal esophagus, respectively (149, 152). To be efficient, the distension must be performed more and more

![Diagram](https://via.placeholder.com/150)

**Fig. 6.** Inhibitory phenomena involved in swallowing. A: inhibition of the activity of esophageal neurons during swallowing. In 1, the *top traces* show the burst firing (SwN) of a late neuron in the dorsal group during swallowing (mylohyoid activity: MHm) elicited by stimulating the SLN. A local distension of the cervical esophagus produced by inflating an intraluminal balloon (indicated by the arrows, EsP: pressure in the esophageal balloon) induces a continuous discharge from the neuron (*bottom traces*). It is worth noting that when a swallow is triggered by stimulating the SLN, the inhibition of the neuronal firing does not occur only during the oropharyngeal stage but starts before the beginning of the swallow. In 2, the *top traces* show the swallowing burst of an esophageal neuron (SwN) during swallowing (MHm) elicited by applying several pulses to the SLN, with a slightly inflated balloon within the hypopharynx (PhP: pressure in the pharyngeal balloon). Note that the swallowing discharge of the neuron is inhibited when the intrapharyngeal balloon is more strongly inflated. [Adapted from Jean (149) (1) and (155) (2).] B and C: field potentials (N) recorded at esophageal sites within the sheep NTS. In B1 and C, stimulation of the SLN induces a single swallow (MHm); note that the potential may be composed of either a single wave (B1) or a biphasic wave in C. The first wave reflects the inhibition of the neuronal population, whereas the second wave indicates that the neuronal excitability has increased. When absent during a single swallow (B1), the second wave can be initiated during rhythmic swallowing (B2), which is known to increase the excitability of the esophageal neurons in anesthetized animals. These recordings suggest that the inhibition of the esophageal neurons during the oropharyngeal stage may be followed by a long-lasting state of increased excitability, which is also triggered by the oropharyngeal stage. (From Jean, unpublished data.) D: intracellular recording of an esophageal motoneuron within the nucleus ambiguous. During swallowing elicited by stimulating the SLN (GHm, Phm, and cEs: EMG of geniohyoid, middle constrictor, and cervical esophagus, respectively), note that the burst firing of the neuron, superimposed on a depolarization of the membrane potential, occurs after a hyperpolarization of the membrane potential, indicating that the neuron has undergone inhibition during the oropharyngeal stage. [Adapted from Zoungrana et al. (377).]
distally as the neuronal discharge occurs later and later during swallowing. Furthermore, the swallowing activity of medullary neurons increases either when a bolus is swallowed or during a subliminal distension of the corresponding region of the tract (149, 152). The burst firing activity of the neuron increases in terms of both its duration and frequency. The changes resulting from peripheral stimulation are more striking in the case of the esophageal than the oropharyngeal neurons: depending on the volume of the balloon inserted, a twofold increase in the duration and a fivefold increase in the frequency can be observed (152). The activation of peripheral receptors during swallowing therefore results in a decrease in the velocity of the peristalsis, which makes the duration of the whole sequence longer and the muscular contraction more powerful. Sensory feedback can therefore be said to modify the central program, by adjusting the motor outputs depending on the contents of the tract (155).

In addition to these excitatory phenomena, the sensory inputs can also trigger inhibitory effects via central connections, as suggested by electromyographic data and vagal motor fiber recordings (129, 276, 281). The occurrence of these inhibitory phenomena has been fully confirmed by microelectrode recordings showing that all the esophageal neurons are strongly inhibited during the oropharyngeal stage of swallowing; they were also inhibited during a pharyngeal distension that stimulated the peripheral receptors (Fig. 6A) (149, 152, 155). Oropharyngeal distension excites the early interneurons, which results in an inhibition of the late and very late neurons via central inhibitory connections. The inhibitory effect depends on the size of the inflated balloon; when it is greatly inflated, swallowing activity is completely abolished, whereas during a slight inflation, this activity is only weakened and delayed (149, 152). The discharge of the very late neurons is also inhibited during the activation of the cervical esophageal receptors. The strength of this inhibition is variable depending on the size of the inflated balloon. These data indicate that the swallowing neurons controlling the distal regions of the swallowing tract are inhibited when neurons controlling the more proximal regions are excited. They support the idea that there may exist a rostrocaudal inhibition within the swallowing network, as suggested by the blockade of the esophageal peristalsis that occurs during rhythmic swallowing (149, 152, 155, 277).

B. Supramedullary Influences on Swallowing

Experimental data have shown that the basic swallowing pattern can be induced without any supramedullary structures being involved. Under physiological conditions, however, the swallowing network receives inputs from higher centers, and several cortical and subcortical structures also influence swallowing (51, 87, 119, 156, 214, 226). The fact that an individual can swallow voluntarily without the existence of any need to ingest food or to protect the upper airways shows that the medullary swallowing network can be activated at least by inputs from the cerebral cortex. In addition, several clinical reports have indicated that cortical dysfunction of the kind resulting from cerebrovascular accidents, cerebral palsy, or neurological diseases such as Parkinsonism, may result in dysphagia or swallowing impairments or may affect esophageal peristalsis (127, 153, 180, 214, 260, 365). These observations point to the involvement of supramedullary influences, although the peripheral afferent pathway and the CPG, which is localized in the caudal brain stem, seem to remain unaltered in these patients.

Supramedullary structures may be responsible for various effects on swallowing such as initiating the motor activity, or modulating reflex swallowing. However, most of the data available were obtained in stimulation experiments and were difficult to interpret, since it is generally not a pure swallowing motor activity that is initiated in this way, but more complex feeding behavior, i.e., mastication and swallowing, or lapping, mastication and swallowing, or licking and swallowing, etc. (42, 316). In addition, it is difficult to identify among these effects those which are due to the afferent feedback and to distinguish between centrally organized movements and motor activities involving feedback phenomena. Moreover, the presumed centrally induced effects may actually arise from the stimulated site or from passing fibers.

There exist a number of subcortical sites, including the corticofugal swallowing pathway, which can trigger or modify swallowing, in particular the internal capsule, subthalamus, amygdala, hypothalamus, substantia nigra, mesencephalic reticular formation, and monoaminergic brain stem nuclei (27, 43, 44, 90, 177, 319–321). These influences can be either excitatory or inhibitory. It has been reported that several forebrain regions, including the amygdala and the lateral hypothalamus, may facilitate swallowing by means of dopaminergic mechanisms (26, 27, 132, 366). Inhibitory effects can be evoked by stimulating brain stem structures such as the periaqueductal gray, the ventrolateral pontine reticular formation, and some monoaminergic cell groups (177, 295, 320, 321). Results suggest that these inhibitory effects probably involve opiate and monoaminergic mechanisms at the level of the NTS (177, 289, 295, 297). Whether these influences act directly on the medullary CPG or may involve a more complex central pathway is not known. Few studies have in fact dealt with these central effects on the neurons of the CPG. As far as the supramedullary influences on swallowing and their action at the cellular brain stem level are concerned, all the results available so far have been obtained in studies on the cortical influences on swallowing.
In several species, swallowing can be initiated by stimulating a limited area of the cortical surface. In rabbits, an efficient region of this kind has been detected within the anterolateral frontal cortex (316). A specific swallowing zone, i.e., one inducing pure swallowing, is situated anterior to the orbital gyrus in sheep (42). It is worth noting that as in the case of peripheral afferent stimulation, swallowing is best initiated by applying repetitive stimulation to the cortex at a frequency in the 20- to 40-Hz range. Recent results have shown, however, in the conscious dog, that a single stimulus applied by transcutaneous magnetic stimulation can induce swallowing (348). Moreover, with the use of this technique, it has been shown in humans that cortical stimulation can produce, as does stimulation of the afferent fibers (see sect. uD1), short-latency electromyographic responses in several oropharyngeal muscles and in the cervical esophagus (119). The corticofugal swallowing pathway, which includes structures such as the internal capsule, the pyramidal pathway, and the mesencephalic reticular formation, ends within the solitary system (43, 44, 159). Lesion of the NTS area involves abolishes the swallowing evoked by cortical stimulation, which further indicates that the solitary system is the main central system responsible for swallowing (152, 159).

Results obtained on anesthetized sheep (152, 159) indicate that most of the early neurons in the DSG can be activated by applying cortical stimulation. This is in agreement with the idea that one of the functions of the cortical area may be to trigger the “voluntary” swallowing motor sequence. Cortically induced swallowing, however, requires repetitive stimulation, whereas a single pulse applied to SLN is generally effective under identical experimental conditions (42, 159). Although direct cortical projections to the NTS have been shown to exist (35, 157, 371), this difference can probably be accounted for by the fact that the pathway from the cortical area to the CPG is polysynaptic (42, 43). Moreover, although all the swallowing neurons with preswallowing activity tested so far have been found to be activated by the cortex, this was so in the case of only 79% of the remaining oropharyngeal neurons studied (152, 159). In line with what occurs with SLN stimulation, cortical stimulation induces an initial activity followed by the swallowing burst that accompanies the onset of swallowing. Both the latency and the number of neurons activated depend on the neuronal group involved. Early neurons in the DSG were cortically activated with a shorter latency than those in the VSG (5-8 ms vs. 10-16 ms), and only 32% of all the neurons in the ventrolateral medulla were cortically activated. Late neurons in the DSG also responded to cortical stimulation, but in small numbers (38%) and with a longer latency of 10-12 ms. None of the late neurons in the VSG nor the very late neurons either in the DSG or the VSG was activated by cortical stimulation (159). Although a direct pathway from the cortex to motoneuronal pools involved in swallowing has been mapped using tracing techniques (184–186), these results indicate that the cortical input to identified swallowing neurons mainly focuses on swallowing neurons in the DSG and involves the same circuit as the afferent fibers do, at least in sheep (Fig. 5). The DSG neurons therefore receive convergent information from both cortical and peripheral inputs that trigger swallowing.

On the basis of the finding that during swallowing sensory feedback is conveyed to the cortical area via a first relay in the pons, the swallowing cortical area may have a further function (48, 160, 320, 321). Neurons in this area may belong to a ponto-cortico-medullary loop so that upon receiving sensory information, they might control the activity of the CPG swallowing neurons as they fire successively, just as peripheral afferent fibers do (159). It has been shown that cortical neurons in the swallowing cortical area of sheep are activated or inhibited during swallowing (45). More recent findings on monkeys indicate that cortical areas associated with feeding behavior may have a further function (48, 160, 320, 321). Neurons in this area may serve mainly to trigger deglutition and control the beginning of the motor sequence, after which the sequence might be carried out without any further cortical control (159).

C. Action of Brain Stem Neurotransmitter Systems

Some pharmacological results relating to swallowing have been reviewed previously (24, 25). The present review focuses mainly on local effects that can be clearly linked to the initiation and programming of the swallowing motor sequence. In this connection, data have been obtained using in situ ejection of drugs by ionophoresis or application of pressure, and most of these results have been obtained at the level of the DSG in rats (24, 25, 161). To date there has been only one study dealing with the action of drugs on functionally identified neurons, i.e., swallowing-related neurons (172). However, other experiments on “reflex” interneurons in the NTS, i.e., neurons which can be synaptically activated via SLN or IX nerves, or on neurons studied in vitro in swallowing medullary regions, have provided some complementary information at the cellular level (161, 298).

At the level of the NTS, i.e., the DSG, experiments based on intracerebral microinjections have yielded deci-
sive information about the involvement of EAA receptors in swallowing mechanisms. In both anesthetized and decerebrate rats, glutamate microinjections performed within the swallowing area of the NTS elicited swallows that were very similar to those triggered by either electrical stimulation of the SLN or mechanical stimulation of the pharyngeal mucosa (Fig. 7A) (124, 173, 178). Both the oropharyngeal stages of swallowing and complete swallowing, i.e., the oropharyngeal stage followed by esophageal peristalsis, can be obtained by performing microinjections into the interstitial NTS subnucleus (173). Specific esophageal peristaltic contractions can be initiated by injecting glutamate and EAA agonists into the region of the subnucleus centralis (23, 124). Furthermore, depending on the dose, glutamate microinjections can induce either a single motor event or series of rhythmic swallowing events similar to those elicited by long repetitive stimulation of the SLN. Microinjections of glutamate are likely to have resulted in generalized neuronal excitation within the area covered by the agent. The fact that these injections into the NTS can produce a patterned response instead of a disorganized muscular activity is quite remarkable and indicates that this region contains neurons that play a prime role in initiating and patterning deglutition and esophageal peristalsis (161). Results obtained using EAA receptor agonists and antagonists have clearly demonstrated that deglutition and esophageal contractions can be triggered by activating either N-methyl-D-aspartate (NMDA) or non-NMDA receptors (124, 173, 178). The effects of NMDA are particularly striking, since

![Diagram of the possible sites of action of excitatory amino acids (EAA) in the swallowing CPG.](http://physrev.physiology.org/)

**FIG. 7.** Effects of neurotransmitter systems on swallowing. **A:** effects of excitatory amino acids. 1: Comparison between the swallowing elicited by stimulating the SLN (top traces: SHm, electromyographic recording of suprathyoid muscles; EsP, intraesophageal pressure recording) and by microinjecting glutamate (25 pmol, 5 nl) into the NTS. 2: Rhythmic swallowing elicited by NTS microinjections of glutamate (500 pmol) and N-methyl-D-aspartate (NMDA; 50 pmol) applied to the same site. Note the inhibition of the respiratory cycle (R, tracheal airflow recording). Only the beginning of the effect of NMDA (total duration, 130 s) is shown. [Adapted from Kessler et al. (173).] **B:** repetitive oropharyngeal swallows evoked by kainic acid applied to the dorsal surface of NTS. Of interest to note that when bicuculline is ejected at an esophageal site within the subnucleus centralis, an esophageal peristalsis occurs after each oropharyngeal stage (Ph, cEs, thEs: intrapharyngeal and intraesophageal pressure recordings, respectively). [Adapted from Wang and Bieger (360).] **C:** inhibitory effects of systemic injection of methscopolamine on esophageal peristalsis. 1: Control swallowing pattern produced by applying electrical stimulation to the solitary complex (Ph, Es: intrapharyngeal and intraesophageal pressure recordings, respectively). 2: Note the inhibition of the esophageal peristalsis after intravenous injection of methscopolamine. [Adapted from Bieger (23).] **D:** diagram of the possible sites of action of transmitters within the swallowing CPG. Excitatory amino acids (EAA) are involved at the NTS level in triggering swallowing. They may be released either by laryngeal afferents or by local glutamatergic neurons. EAA are also involved in the transfer of the swallowing drive from the NTS neurons to interneurons in the ventrolateral medulla (VLM) and motoneurons (Mn) in the nucleus ambiguus. The pathway may involve only EAA or synapses with unknown transmitters. The connections between oropharyngeal (OP) and esophageal (Es) NTS neurons may involve both GABA and acetylcholine, in the case of inhibitory and excitatory connections respectively (see text for comments).
this agent can elicit long series of rhythmic swallows, including more than 100 motor events (178). At esophageal sites, activation of NMDA receptors seems to be more potent than that of non-NMDA receptors (24). This is in keeping with the existence of large numbers of NMDA receptors within the subnucleus centralis (40). At the cellular level, it has been reported that glutamate activated almost all the reflex neurons tested (130, 298). With the use of brain stem slices, it has been found that neurons located in NTS regions known to contain swallowing neurons possess both types of EAA receptors (330).

Within the DSG, EAA mechanisms may contribute to initiating the motor sequence and to building up the swallowing pattern. EAA may be released either by afferent fibers involved in swallowing or by intrinsic NTS neurons, or both (Fig. 7D). Although there is no direct evidence that swallowing afferent fibers actually use EAA as a transmitter, microinjections of either DL-2-amino-5-phosphonovalerate (APV), a NMDA receptor antagonist, or 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-NMDA receptor antagonist, performed within the NTS of decerebrate rats can result in the complete disappearance of the SLN-induced deglutition as well as esophageal reflex responses (161, 203). It has also been established using immunohistochemical or retrograde tritiated aspartate transport methods that glossopharyngeal and vagal afferent fibers in addition to other neurotransmitters may use EAA as transmitters (251, 286, 287, 290, 291). Moreover, results obtained by combining retrograde transport of tritiated aspartate with peroxidase immunohistochemistry or fluorogold histofluorescence have suggested that SLN afferent fibers may use EAA as transmitters (N. Schaffar and A. Jean, unpublished results). As is the case for baroreceptors and some vagal pulmonary afferent fibers (33, 168, 274, 351), it is therefore likely that at least some of the afferent fibers involved in the initiation of swallowing may use EAA as transmitters. In addition, glutamatergic NTS neurons have been found to exist and may be activated by the afferent fibers (179, 286, 324). The possibility that EAA receptors may be involved in patterned swallowing has been strongly supported by the results of experiments where an oscillatory behavior, i.e., rhythmic swallowing or rhythmic esophageal contractions, was induced by locally applying EAA (Fig. 7, A and B) (124, 178). Studies on brain stem slices have shown that NTS neurons exhibit EAA-induced rhythmic patterns of activity that paralleled those of swallowing neurons and have pacemaker properties that were activated via NMDA-receptor associated channels (Fig. 9A). These studies suggest that EAA receptors may play a critical role in the motor patterning of swallowing behavior (332, 333).

EAA receptors are involved in swallowing not only within the DSG, but also at the level of the VSG and the motoneurons (Table 2). However, the effects of EAA at the ventral level have been less fully documented. Microinjections performed in vivo failed to elicit the oscillatory behavior characteristic of rhythmic swallowing (24). Results obtained by Kessler (172) have indicated that the swallowing activity of neurons in the VSG depends on the activation of EAA receptors, that is to say that the swallowing drive set up in the DSG and transferred to the swallowing neurons in the VSG involves at least the EAA (Fig. 7D). This result is in keeping with anatomical data showing the existence of glutamatergic connections between NTS and ventrolateral medulla (307). Here again, both types of EAA receptors, i.e., NMDA and non-NMDA receptors, are involved. In studies on brain stem slices, it has been established that the NMDA receptors play a critical but paradoxical role, since they are involved in the rising phase of the excitatory postsynaptic potentials elicited in these neurons in response to stimulation applied to the solitario-ambiguous pathway (361).

Inhibitory phenomena are thought to play an important role in the swallowing mechanisms (see sect. V). However, little is known so far about the function of neurotransmitters such as inhibitory amino acids in deglutition. Some of the most interesting results in this field have been those obtained by Wang and Bieger (360), who observed that microinjections of GABA or GABA$_\alpha$ agonist such as muscimol inhibited the motor events associated with swallowing and esophageal peristalsis. It has also been reported that local application of bicuculline at the NTS level induced either rhythmic swallowing or rhythmic esophageal peristalsis, which suggests that a tonic inhibitory action is exerted by GABA neurons on the swallowing pattern generator. Some other features relevant to the coupling between the oropharyngeal stage of swallowing and esophageal peristalsis have been consistently described in these experiments. When swallows consist of oropharyngeal stages alone, local application of subthreshold doses of bicuculline can render the swallows complete, i.e., the oropharyngeal phase is followed by primary peristalsis (Fig. 7B). Moreover, during fast rhythmic swallowing, which normally consists of a series of oropharyngeal stages alone, application of bicuculline can release the inhibition, preventing the occurrence of esophageal phases, and complete rhythmic swallows occur. Among the many possible explanations, the most plausible one seems to be that GABAergic mechanisms may be involved in the inhibition of the esophageal phase of swallowing that occurs during the oropharyngeal phase (Fig. 7D and Table 2). The exact origin of these GABA-mediated inhibitory phenomena is unknown, but local GABAergic NTS neurons are probably involved (32, 144, 209, 216, 325). In addition, recent results have shown that neurons within the subnucleus centralis, which are thought to be esophageal premotor neurons, express GABA$_\alpha$ receptor subunits (38). These results therefore suggest that inhibitory amino acids probably play an im-
portant role in the inhibitory mechanisms at work within the swallowing network (133). At the ambiguous level, stimulation of GABA_A receptors has been found to modulate the excitatory action of EAA and acetylcholine. Thus it seems highly probable that the inhibitory amino acids also intervene at this level (24).

Cholinergeric neurotransmission has also been found to play a role in swallowing mechanisms, particularly those underlying esophageal peristalsis (23, 204). At the level of the NTS, esophageal contractions can be induced by locally applying acetylcholine or muscarinic receptor agonists. Moreover, the esophageal stage of a swallowing sequence can be blocked after local application of muscarinic antagonists, such as methscopolamine, within the NTS (Fig. 7C). These results suggest that a cholinergeric mechanism probably participates in the linkage between the oropharyngeal and esophageal stages of swallowing (Fig. 7D and Table 2). Systemic injections of atropine have also been found to block the esophageal stage of swallowing in sheep (376). However, the cholineric link between the oropharyngeal and esophageal activity might be species dependent and requires further investigation. In cats and humans, atropine injection does not block the esophageal peristalsis of the striated portion of the esophagus, which suggests that central muscarinic receptors are not involved in the pharyngo-esophageal coupling (31, 114, 262). The source of cholineric inputs to NTS has not yet been clearly identified. Cross-innervation and immunohistochemical data have suggested that vagal afferent fibers may use acetylcholine as a transmitter and that some of these fibers might be esophageal afferent fibers (97, 261). It has also been demonstrated that NTS neurons receive a cholineric input from neurons in the intermediate zone of the parvcellular reticular formation. Anatomical and electropharmacological data suggest that this projection may be involved in esophageal motility (25, 203). The cholineric input may also arise from intrinsic neurons that have been identified within the NTS using choline acetyltransferase immunohistochemical procedures (285). Cholinergeric transmission has also been found to take place via esophageal motoneurons. Acetylcholine applied to the ventrolateral medulla induces esophageal contractions, probably as the result of depolarization of esophageal motoneurons tentatively identified in brain stem slices (25). The acetylcholine-induced effects on esophageal motoneurons are resistant to muscarinic antagonists and depend on nicotinic receptors (362, 375), which have been shown to participate in esophageal peristalsis (114).

The role played by monoamines in central swallowing mechanisms was first investigated by means of indirect methods such as those based on the use of systemic injections or the intracerebroventricular application of drugs (24). Under these experimental conditions, excitatory effects of monoamines have been observed. Precur-

sors or agonists can either induce the swallowing motor pattern or facilitate the effects of laryngeal stimulation or the occurrence of spontaneous swallows (24). On the other hand, results obtained by performing microinjections of monoamines into the swallowing NTS area have shown that monoamines have mainly depressant effects on swallowing, i.e., they resulted in reversible, dose-related decreases in both the number and strength of the rhythmic swallows elicited by ipsilateral SLN stimulation (175–177). This inhibitory action is not a side effect due to the perturbation of homeostatic parameters such as respiratory rhythm or blood pressure, since the swallowing elicited by stimulating the SLN contralateral to the injection site remained unaffected.

With regard to the catecholamines, the inhibitory action of norepinephrine can be mimicked by clonidine microinjection and reduced by pretreatment with phenolamine, but not with metetiprin, a serotoninergic blocker (176). It is therefore likely to result at least partly from activation of α-adrenergic receptors. The nature of the receptor involved in the effects of dopamine is still unknown. It should, however, be noted that microinjections of the dopaminergic agonist apomorphine also inhibit swallowing (176). These data indicate that catecholamines exert an inhibitory influence on the NTS neural components involved in deglutition, and as yet, there is no direct evidence available that any excitatory effects may be exerted at this level. It is likely that the facilitatory effects elicited by systemic administration might originate from the drugs acting on supramedullary structures, as suggested by experiments in which catecholamines, in particular dopamine, locally applied to several forebrain regions, were found to have a facilitatory action (26, 27, 29, 366). Results show that apomorphine exerts a facilitatory influence on swallowing when injected into the internal carotid artery, but an inhibitory effect when injected via the vertebral artery. It can therefore be postulated that by acting on forebrain sites, catecholamines have facilitatory effects on swallowing, whereas they have inhibitory effects when released locally at brain stem levels, particularly in the NTS. Ionophoretic application of catecholamines within this region has a mainly depressant effect on neuronal activity (54).

Local applications of serotonin have been reported to have either inhibitory or excitatory effects on swallowing (123, 175). One should note, however, that ionophoretic application of serotonin or serotonergic agents to NTS neurons, particularly the reflex neurons, consistently inhibits the neuronal activity (100, 297, 298). The antagonistic effects on swallowing are certainly due to differences in the neuronal sensitivity to serotonin and are therefore likely to have resulted from different receptor subsets being activated. The excitatory effects may be mediated by 5-HT_2 receptors, since they are abolished by intravenous injection of either ketanserin, methysergide, or...
mtergoline (24). The nature of the receptor(s) mediating the depressant action of serotonin has not yet been clearly established. This effect is mimicked by quipazine and 5-hydroxy-2-(di-N-propylamino)tetratin (8-OH-DPAT) and can be partially prevented by local pretreatment with meteptin, but not by intravenous injections of methysergide and metergoline. These results suggest that 5-HT1 receptors are involved (161), which is in line with the recent finding that 5-HT1A binding sites exist in high densities in NTS areas involved in deglutition (210, 334). The question as to what exact factors determine the effects of serotonin, i.e., excitation versus inhibition, have not yet been elucidated. Due to serotoninergic receptors having differential affinities, the amount of agent microinjected may be a critical factor. The neural components involved in these opposite effects may also be different. The respective distributions of the injection sites involved in excitatory and inhibitory effects only partly overlap. The inhibitory sites are located in the NTS regions known to contain swallowing neurons receiving laryngeal inputs, i.e., at the level of the interstitial subnucleus, whereas the excitatory sites are located more rostrally and more medially (161).

The effects of monoamines on swallowing may be mediated by intrinsic catecholaminergic NTS neurons belonging to groups A2 and C2 and a population of serotonin-containing neurons identified in the rostromedial NTS (134, 135, 165, 166). Indeed, vagal afferent fibers have been found to impinge on catecholaminergic neurons in the NTS (312). In addition, some vagal afferents have been found to use serotonin as a transmitter (104, 250). One relevant finding in this connection was that when electrical stimulation was applied to several brain stem regions containing either catecholaminergic or serotoninergic cell groups, such as the raphe magnus, the ventrolateral reticular formation at the pontine and bulbar level, and the locus coeruleus, it inhibited reflex deglutition (177). The existence of catecholamine- or serotonin-containing projections arising from some of these regions and terminating in the NTS has been established in several anatomical studies (289, 335). It can therefore be postulated that the swallowing inhibition observed in response to stimulation of brain stem monoaminergic nuclei may at least partly result from a release of catecholamines or serotonin within the NTS. It is worth pointing out that when applied to the locus coeruleus and the raphe magnus, electrical stimulation also depolarizes the laryngeal afferent fibers (205). This suggests that the inhibition of reflex deglutition, whether it results from brain stem stimulation or is induced by monoamine microinjection into the NTS, may at least partly depend on a blockade of peripheral inputs.

Preliminary evidence is now available which suggests the existence of excitatory or inhibitory peptidergic mechanisms affecting swallowing. An excitatory action has been observed with thyrotropin-releasing hormone, vasopressin, oxytocin, and somatostatin (24). In the latter case, anatomical studies have shown that a somatostatinergic connection runs between the NTS subnucleus centralis, where esophageal neurons are assumed to be located, and the compact rostral formation of the nucleus ambiguus, which contains esophageal motoneurons (36, 71). It has been established moreover that somatostatin regulates neurotransmission mechanisms at the level of ambigual motoneurons by facilitating glutamate-induced excitation and depressing acetylcholine-induced excitation, two excitatory effects which are thought to be involved in the swallowing mechanisms (363, 364). Somatostatin therefore probably has neuromodulatory effects on the swallowing network. The inhibitory effects of peptides on swallowing have been found to involve opioid receptors such as the µ, δ, and κ binding sites (24). The opiates may act at the DSG, VSG, and motoneuron levels, where a high density of enkephalinergic terminals has been found to exist, particularly within the compact rostral formation of the nucleus ambiguus (232).

More recent results, based on chemical neuroanatomical techniques, have shown that neurons, in the NTS subnucleus centralis, which project to the rostral compact formation of the nucleus ambiguus and which are probably premotor esophageal neurons, can synthesize nitric oxide (37, 103, 370). The role of these neurons in central swallowing mechanisms now is required to be investigated.

V. NEURAL MECHANISMS

A. Central Pattern Generation

The central mechanisms that generate the bursting activity of swallowing neurons and their sequential or rhythmic firing behavior are still unknown. In the light of the latest mechanisms found to be responsible for pattern generation in several other CPGs, it seems likely however that the shaping and timing of the deglutitive motor pattern is based on the connectivity and the synaptic interactions between the various groups of neurons in the network, and the intrinsic properties of neurons (77, 107, 108, 115–117, 197, 265, 292). Although little direct evidence is available as to the exact nature of the swallowing patterning mechanisms, the body of data which has been built up in this field over the past 25 years provides valuable information about the functional mechanisms possibly underlying the central organization of swallowing.

1. Network properties: role of excitatory and inhibitory phenomena

The fundamental act of swallowing, in particular its oropharyngeal stage, is a stereotyped motor behavior, and
the swallowing CPG has been viewed classically like a dedicated circuit, i.e., like a specific network of neurons which is hardwired so as to produce a sequence of excitation and inhibition that is always the same (51, 87, 152, 154, 226, 277). The CPG must be able to perform a wide range of tasks, such as converting the repetitive messages conveyed by central or peripheral afferent inputs into a bursting activity, transmitting bursting activity after a variably long delay depending on the nature (oropharyngeal or esophageal) of the neuron in the network, ensuring via a rostrocaudal inhibitory mechanism that the later neurons cannot fire before or during the activity of the earlier neurons, and generating a rhythmic bursting pattern, at least in the case of the oropharyngeal neurons.

The bursting pattern of the swallowing neurons may be built up as the result of either reexcitation phenomena or excitatory feedback mechanisms (107, 108). The centrally generated bursting pattern of swallowing NTS neurons suggests that these mechanisms may well take place within the DSG. Neurons with preswallowing activity presumably possess these reexcitation loops so that the neuronal firing will increase until reaching the critical level at which the swallowing burst is generated (Fig. 4, C and D) (149, 152). The rhythmic firing pattern of the oropharyngeal neurons may rely either on a specific network arrangement, which still remains to be determined, and/or on cellular properties of the neurons (see sect. vA2).

In addition to the mechanisms by which is generated the burst firing of the swallowing neurons, the swallowing network can be viewed as a linear-like chain of neurons based on the rostrocaudal anatomy of the swallowing tract. Because there exist, within the NTS, neurons which fire sequentially during swallowing, each neuron or group of neurons in this chain may control more and more distal regions of the swallowing canal and be responsible for the successive firing behavior (Fig. 8A) (152, 154, 277). Excitatory connections between neurons may provide the basis for the successive excitation of the cells via increasingly numerous polysynaptic connections. There is no direct evidence available so far about connections between identified swallowing NTS neurons. However, recent anatomical data show that such connections may exist between neurons located in the interstitial and centralis subnuclei of the NTS (39). In addition to the central connections, each DSG neuron in the chain may be synaptically activated via peripheral afferent fibers originating in the corresponding part of the tract which is under their control. Whether or not this linear pattern of organization in the form of a chain of neurons exists at the VSG level also has not yet been ascertained. This actually seems rather unlikely, since central stimulation experiments and those involving the application of EAA in the ventrolateral medulla have failed so far to elicit an organized swallowing motor pattern (24, 161).

In addition to excitatory connections, there also exist inhibitory connections between the various links in the chain. It has been reported that when the neurons responsible for the beginning of the swallowing sequence fire, the cells controlling the more distal parts of the tract are inhibited, and their activity is delayed (149, 152). In this way, inhibition is also successively transmitted throughout the network. Inhibitory phenomena play an important role in the shaping and timing of the sequence, since the neurons controlling more distal parts of the swallowing canal are subjected to longer periods of inhibition than those controlling rostral parts (149, 152). Because no neurons have ever been observed that start to discharge at the onset of swallowing and fire for longer periods when they control more distal parts of the tract, the long-lasting inhibition exerted on the late and very late neurons may result from the successive additional periods of inhibition triggered within the chain by the neuron that is active (Fig. 8A). The inhibitory message that no doubt occurs before the excitatory transfer of the bursting discharge seems to play an important role in the central mechanisms. In fact, leaving aside the neurons with preswallowing activity, recordings of the motor events and the central neuronal activity have suggested that the inhibitory phenomena may be the first events initiated in the network (87). In the absence of intracellular recordings, it is not yet possible to state whether or not hyperpolarization may occur before the bursting discharge of the swallowing neurons. Extracellular recordings have shown, however, that the activity of distal neurons is inhibited before the motor activity is initiated (see Fig. 6A). In addition, a subliminal SLN stimulation that does not induce swallowing has been found to, nevertheless, induce inhibitory phenomena such as relaxation of the lower esophageal sphincter (263). Recent studies in humans, using an artificial high-pressure zone created by inflating an intraesophageal balloon, suggest that a wave of inhibition occurs before the esophagus contracts (303, 304). Furthermore, IX stimulation, which activates the preswallowing neurons to a subcritical level as far as the initiation of swallowing is concerned, nevertheless inhibits the esophageal neurons (61). Recent intracellular studies on esophageal motoneurons have confirmed these assumptions. Their authors have demonstrated that these inhibitory phenomena are also present at the motoneuronal level, which means that not only excitatory inputs but also inhibitory messages are transferred from the NTS to the motoneuronal level (Fig. 6D) (376, 377).

Inhibitory mechanisms may not only be responsible for delaying the onset of neuronal firing, but they may also contribute directly to the sequential excitation of the neurons. In fact, via mechanisms such as disinhibition or postinhibitory rebounds, the inhibitory connections may be at least partly responsible for the progression of the contraction wave. With the assumption that there exist only inhibitory connections between swallowing neurons
Fig. 8. Possible mechanisms involved in pattern generation. A: the swallowing network can be viewed as a chain of neurons (1-4) that parallels the rostrocaudal anatomy of the swallowing tract. When triggered by peripheral or central inputs, the neurons at the beginning of the chain (1) generate, on the basis of network and/or cellular properties, a burst firing which starts the sequence; they also exert inhibitory effects on the more caudal neurons in the chain (2, 3, and 4) through central inhibitory connections (lines with black dots). The swallowing drive may be transferred by central excitatory connections (white triangles) to the subsequent neuron in the chain (2), which also inhibits the more caudal neurons, etc. The sequential firing behavior therefore results from the successive excitation of the neurons paralleled by a rostrocaudal inhibition, which lasts longer when the neuron is more distal in the chain. This network may function without any sensory feedback, but the peripheral inputs may modulate the sequence (broken lines). Intrinsic properties of the neurons such as pacemaker, postinhibitory rebound, and delayed excitation properties may intervene in the functioning of the chain (see text). Given this scheme of organization, it can be postulated to account for the differences between primary and secondary peristalsis, that the strength of the central excitatory connections decreases in the caudal direction, while the afferent feedback inputs then become more important (see text for comments). [Adapted from Jean (155)]. B: the chain may also function mainly on the basis of inhibitory connections. In this case, the sequential firing of the neurons may be produced mainly by mechanisms such as postinhibitory rebounds. In this case again, these mechanisms will presumably decrease as they occur more caudally. As suggested by field potential recordings, it can be postulated that the neurons generating the oropharyngeal stage can also induce, in addition to the inhibition, a long-lasting excitatory influence on neurons of the esophageal network, indicated here by the dotted line with striped triangles (see text for further information). The sequential firing is therefore dependent on both the inhibitory connections and the properties of the neurons and on a facilitatory influence exerted on the esophageal network in the case of the primary peristalsis. This tentative mechanism of intrinsic modulation may account for the differences between primary and secondary peristalsis. The traces below the diagrams give the membrane potential of oropharyngeal (1) and esophageal neurons (2, 3, and 4). The upward deflection corresponds to a depolarization of the neuron and the downward deflection to an hyperpolarization. The dotted lines in B show a possible long-lasting excitatory or facilitatory influence exerted by the oropharyngeal neurons on the esophageal ones.

(Fig. 8B), the sequential excitation of neurons may result from postinhibitory rebounds involving in this case cellular properties of the neurons in addition to network connections (see sect. VA2). It is also possible that the strong inhibition generated during the oropharyngeal stage of swallowing may be followed by long-lasting excitatory or facilitatory effects exerted by the oropharyngeal neurons on the esophageal network, resulting in the sequential discharge of the neurons (Fig. 8B). Results obtained at the network level support both of these hypotheses. It has been reported that a subthreshold distension of the esophagus, which gives rise to no contractions of the tract, can elicit a contraction at the segmental level when electrical stimulation applied to the IX nerve is withdrawn.
In this case, the IX nerve exerts only inhibitory effects at the level of the esophageal neurons, and the contraction therefore results from postinhibitory rebound mechanisms; it is the inhibition that renders the subthreshold distension effective. Field potentials recorded at the level of esophageal neurons in the NTS may be composed of either a single wave of potential reflecting the inhibition of these neurons during the oropharyngeal phase of swallowing, or a biphasic wave of potential indicating that the esophageal neuronal population is undergoing an excitatory or a facilitatory influence following the inhibition (Fig. 6, B and C) (152). Therefore, the biphasic wave of potential reflects an inhibitory-excitatory sequence occurring at the level of the esophageal neurons during swallowing. It is of interest that the wave of excitation is not systematically present, like the esophageal stage in anesthetized preparations. Moreover, it gradually becomes stronger during rhythmic swallowing, which is known to facilitate complete esophageal peristalsis in experimental animals (Fig. 6B). The wave of excitation reflecting the activity of esophageal neurons may depend on some rebound phenomena or result from a state of excitation that may be induced by the release of a neurotransmitter with a long-lasting action during the oropharyngeal phase. Consequently, the oropharyngeal stage of swallowing may trigger phenomena such as intrinsic neuromodulation (170), i.e., the activity within the network of oropharyngeal neurons may facilitate that of other neurons within the network, namely, the esophageal neurons.

2. Cellular properties: intrinsic and transmitter-induced properties

Most of the data on the intrinsic properties of neurons liable to be involved in swallowing have been obtained in studies on brain stem slices. The data indicate that neurons located in dorsal and ventral medullary regions and in cranial motor nuclei that are involved in swallowing, such as V, VII, X, and XII motor nuclei and the nucleus ambiguous, possess various ionic conductances that may be involved in patterning the swallowing motor event (55, 56, 58, 74, 75, 118, 332, 333, 340, 354, 355, 374). The linkage between the endogenous properties of neurons studied under these in vitro conditions and their possible role in swallowing pattern generation is far from having been elucidated at present. The most relevant data in this connection have been obtained in studies on NTS neurons, in particular those located in the peri-interstitial region of the NTS where are situated swallowing-related neurons (330–333).

Extracellular recordings on neurons in the rat NTS region have shown that repetitive stimulation applied to afferent fibers within the tractus solitarius can elicit bursting discharges in some NTS neurons (329, 331). In terms of the duration of the discharges and their bursting frequency, some of these discharge patterns look like those of swallowing neurons (161, 327). Results obtained with bath application of EAA have shown that specific activation of NMDA receptors can induce rhythmic bursting patterns in NTS neurons (330, 331). Here again, some of the patterns resemble those of swallowing neurons in terms of the bursting discharge and bursting frequency. There is admittedly no definite evidence available so far that these neurons may be swallowing neurons, but at least it can be said that within the swallowing-related NTS regions, there are neurons present that respond in vitro just like the swallowing neurons respond to afferent stimulation and NMDA application in vivo.

Intrinsic neuronal properties have been thoroughly documented in slice preparations by performing intracellular recordings. Like most of the neurons in the central nervous system of mammals, NTS neurons have been found to have several endogenous properties, some of which seem to be relevant to swallowing pattern generation (161, 327). NTS neurons possess an early transient outward potassium current (IKA) that is responsible, in addition to its role in frequency adaptation, for the delayed firing of the neurons that occurs when they are depolarized from negative membrane potentials (75, 332, 333). IKA might therefore be involved in the sequential activity of swallowing neurons. If there exist any cells with an IKA conductance within the swallowing network, it is possible that inhibition of these neurons might abolish the steady-state inactivation of IKA, and therefore delay the onset of their firing. It should be noted that the delay induced by IKA is dependent on the inhibitory effects: the stronger the hyperpolarization of the neuron, or the longer its duration, the longer this delay will be. A neuron subjected to a short inhibition will therefore fire earlier than one influenced by long-lasting inhibition (Fig. 9B) (327). The pattern of activity of esophageal neurons fits this picture very well. Within the swallowing net, IKA conductances might therefore contribute to the delayed activation of the neurons. It should be pointed out, however, that the neurons must receive excitation to be able to produce their burst firing activity. Within a network of neurons with excitatory connections between them, excitation is sequentially transferred, and the IKA conductances may adjust the sequential firing of neurons. If the excitation results mainly from long-lasting excitatory effects developed during the oropharyngeal stage, i.e., from the hypothetical intrinsic system of modulation, the IKA conductances will play a key role in the delayed firing of the neurons. In this case, it is of interest to note that the network may function mainly with inhibitory connections (Fig. 8B). It has also been reported that some NTS neurons possess low-threshold activated calcium currents, I(TCa), which are responsible for postinhibitory rebounds (Fig. 9C) (56, 328). If some neurons in the swallowing
network do have these calcium conductances, it is therefore likely that they will be involved in their burst firing activity. As stated above, most of the neurons in the swallowing CPG probably undergo inhibitory influences before their burst firing is initiated. These inhibitory inputs may therefore activate the \( I_{T(Ca)} \) and participate in the bursting activity. Moreover, as postulated above, with properties of this kind, the swallowing network will be able to function only if there are inhibitory connections between the neurons. Whether or not this is the case, the sequential firing of the neurons will therefore rely mainly on the postinhibitory rebound properties of the neurons. Moreover, the responses of NTS neurons to activation of NMDA receptors have shown that they have pacemaker-like properties (Fig. 9, A and D) (332, 333, 356). In addition to mechanisms such as those involving reexcitation phenomena, if swallowing neurons possess these pacemaker-like properties, it is very likely that they may participate in burst generation, as has been found to occur in several other CPGs (11, 117, 358). Interestingly, the NMDA-induced bursting pattern is dependent on the membrane potential and occurs in a high membrane potential range (333, 356); this feature is in keeping with results suggesting that the bursting swallowing pattern is preceded by an inhibitory phase. It is therefore likely that NMDA-gated conductances may participate in the burst formation within the swallowing network. Because NMDA receptors are actually involved in generating de-
glutition, or more specifically, rhythmic swallowing and in eliciting pacemaker-like properties in NTS neurons, it is furthermore likely that the oscillatory properties of the swallowing network may involve conditional bursters located within the NTS. In fact, two types of NMDA-induced bursting patterns have been recorded among NTS neurons (Fig. 9A) (332). The one pattern corresponds to a typical pacemaker bursting activity, in which the firing of the neuron is superimposed on a bell-shaped depolarization of the membrane potential. Due to the limited samples of this type of neuron available, the conductances involved in the burst firing have yet not been specified, however. The other pattern of pacemaker-like oscillations results in the activation of NMDA-gated conductances and in interactions with other voltage-dependent conductances at work in NTS neurons, such as high-threshold calcium conductances, calcium-activated potassium currents, and $I_{KA}$ (Fig. 9D). In this case, the burst firing is subtended by a wave of depolarization with a characteristic ramp-shaped phase, the duration of which increases with the hyperpolarization and thus delays the firing. These interactions between chemo- and voltage-gated conductances have been found to play a key role in the expression and shaping of the cell discharge pattern (333).

**B. Mechanisms of Deglutition and Secondary Peristalsis**

In species with an entirely striated esophagus, it has by now been clearly established that deglutition, i.e., the oropharyngeal phase followed by primary peristalsis, is a centrally patterned motor activity and that the central program is modulated by central or peripheral inputs so that the motor contraction is adapted to the size of the bolus (see sect. iv). In species with a smooth muscle esophagus, intrinsic peripheral mechanisms of both neural and muscular origin are obviously involved in the organization of the smooth muscle motor pattern (78, 79, 80, 110, 111, 280). Even in this case, however, several data have suggested that under physiological conditions the central nervous system may also contribute to the organization of the sequential motor pattern (145–148, 336). A good example of this central intervention has been provided by experiments showing that sequential activity occurs in vagal preganglionic fibers during swallowing (109, 281). It is therefore to be expected that when activated, the CPG will always organize the whole sequence from the oropharynx to the esophagus. The hypothesis that the network consists of a chain of neurons would account for how this sequence is generated. However, there exist some differences between the oropharyngeal and esophageal phases of swallowing. In fact, results indicate that unlike the oropharyngeal phase, the esophageal phase may show some lability and also suggest that the central program controlling this phase may be less robust than that responsible for the oropharyngeal phase (see sects. ii and iii). The size of the neuronal population involved during these two phases is also different. Depending on the number of muscles involved, the number of active neurons during the oropharyngeal phase of swallowing has been found to be far larger than that involved in the esophageal phase (149, 152). The bursting activity of the oropharyngeal neurons is also very different from that of the esophageal neurons. Among the motoneurons, the only respect in which the two types differ is the duration of the discharge, whereas among the interneurons, the discharge frequency also differs conspicuously, since it can be 10-fold higher in the case of the oropharyngeal neurons. It is also worth noting that even when the discharge frequencies were in the same range of magnitude, as in the case of the late and very late neurons, there was also a significant difference between the frequencies, the higher frequency being that observed in the neurons controlling the proximal parts of the esophagus (149, 152). A clear-cut discharge frequency gradient can therefore be said to exist within the swallowing network, and the elements subserving these two stages are clearly quite separate. Whatever mechanisms may be involved in the sequential firing, their strength therefore obviously decreases along the chain of neurons. These differences may reflect differences in the strength of the synaptic connections along the chain of neurons, possibly due to the existence of increasing numbers of synapses, and/or to the properties of the cells. In fact, data obtained in the case of secondary peristalsis have suggested that the swallowing CPG can be subdivided into two subnetworks: an oropharyngeal and an esophageal net of neurons, each of which mediates the patterning of the respective phase of deglutition, but that the esophageal net is likely to have less robust central mechanisms and be more dependent on afferent inputs.

The mechanisms underlying secondary peristalsis have not yet been completely elucidated. In some species, no clear-cut differences have been observed between the primary and secondary peristaltic processes (141, 147, 148, 199, 302), whereas in others, striking differences have been noted, since the secondary peristalsis hardly depends at all on afferent feedback (152, 219, 220, 277). Whatever mechanisms may be involved, secondary peristalsis functions most efficiently with continuous feedback. In sheep, for example, the fact that secondary peristalsis is obviously dependent on feedback phenomena suggests that there is little if any central programming and that the sequential contractions rely on peripheral feedback mechanisms (152). This also supports the view that the esophageal net is completely separate from the oropharyngeal one. However, authors performing microelectrode recordings failed to detect any differences between
the neurons involved or their discharge parameters: a given neuron was found to be involved in both primary and secondary peristalsis, and the duration of discharge and the frequency were the same in both cases, or even more paradoxically, were larger during secondary peristalsis (149, 152). This is puzzling from the patterning point of view. Why are afferent inputs necessary under these conditions, and why is the central program ineffective? In fact, when the same elements are involved in both cases without there being any difference between their discharge patterns, the sole difference between primary and secondary peristalsis is that the latter lacks an oropharyngeal phase, and consequently is not accompanied by any oropharyngeal network activity. Therefore, the activity of the oropharyngeal net might be an important factor in the central programming of primary peristalsis. That is to say that the esophageal net may program esophageal peristalsis only when triggered by the oropharyngeal net. In this way, the oropharyngeal net may serve as an intrinsic modulatory system (Fig. 8B), a mechanism which seems to play an important role in several CPGs (170). When it is present, the esophageal net can program the peristaltic wave, whereas when it is absent, as in the case of secondary peristalsis, the program requires peripheral influences. Whatever the case may be, the previous oropharyngeal phase will facilitate or trigger central esophageal programming mechanisms, such as those involving the powerful inhibitory phenomena which induce postinhibitory rebounds and/or long-lasting facilitatory influences.

C. Nature of the Swallowing CPG

Classically, the swallowing CPG has always been taken to be a specific network of neurons dedicated to this function alone. However, this view has by now been challenged in the light of numerous data obtained mainly on the central nervous system of invertebrates. In addition to being a classical dedicated network, most of the CPGs seem in fact to be either reorganizing or distributed circuits, and a single neural circuit can combine features typical of each of these different architectures (82, 169, 237, 265). In any case, it has been established in particular in the case of the crustacean pyloric pattern generator that various pattern generators exhibit a high degree of flexibility, resulting in considerable functional plasticity (82). This is a particularly relevant point in the case of the swallowing CPG for the following reasons. Although the flexibility of the motor pattern generators has been clearly demonstrated in invertebrates, several examples have by now come to light which suggest that in vertebrates, particularly in mammals, pattern generators also show some flexibility (237, 265). Previous results relating, for example, to the cellular properties of neurons have shown that mechanisms found to operate mainly in the central nervous system of lower species are equally valid in the case of mammalian central nervous system (197). The swallowing CPG is not an automatic, continuously functioning CPG, and the question arises as to whether the swallowing neurons are completely inactive when no swallowing occurs, or whether these neurons may have other functions. This question is especially interesting, since we have established that swallowing neurons include NTS neurons, and it has by now emerged that the NTS is far from being simply a sensory relay (157, 161). NTS neurons are involved in many activities, such as the autonomic ones, as well as in endocrine processes and in several integrated behaviors such as emotional processes, hunger, thirst, control of pain mechanisms, regulation of the level of consciousness, and probably many other yet nonidentified functions (157). This is particularly striking given that the NTS is quite a small structure containing only a small population of neurons, numbering around 40,000 in the case of the rat caudal NTS (259). Are all the NTS neurons in this very small population each devoted to a single fixed function, or do there exist within the NTS one or several populations of neurons that are flexible and participate in several functions, depending on the inputs they receive? It has been observed by the group of Maurice Moulins that in invertebrates, swallowing depends on a pattern generator that is temporarily formed preparatory to the production of the motor activity (222, 223). That is to say that when a given stimulus is delivered, a pool of appropriate neurons is activated and forms the swallowing CPG, whereas these neurons are involved in other tasks when no swallowing activity is required.

In keeping with the new principles involving flexible circuits, recent results have suggested that within the swallowing CPG, some neurons may participate in activities other than just swallowing-related ones. It has been established that not only motoneurons, but also interneurons can be involved in at least two different tasks, such as swallowing and respiration, swallowing and mastication, or swallowing and vocalization.

With regard to the swallowing motoneurons, some recent results have indicated that ambigual, trigeminal, and hypoglossal motoneurons can fire both in phase with respiration and during deglutition, as well as with swallowing and mastication, swallowing and vocalization, and even during swallowing, vocalization, and respiration (3, 190, 300, 313, 317, 318, 323, 346, 376). Therefore, common motoneurons may be involved in these activities. By driving muscles that can participate in two or more activities, these motoneurons probably participate in the fine tuning of the muscular activity during the motor behavior. These motoneurons presumably receive a drive from separate CPGs, and their activity no doubt depends on synaptic interactions between the two networks.
Some recent results have indicated that interneurons localized in the dorsal (DSG) or ventral (VSG) regions of the swallowing network also fire during several motor behaviors such as swallowing, respiration, mastication, and vocalization (Fig. 10, A and B) (7, 22, 59, 106, 172, 190, 252, 253, 373). The common motoneurons might therefore be triggered by common pools of interneurons. These results indicate that in mammals, the neurons liable to be involved in pattern generation can belong to different CPGs. Multifunctional neurons of this kind would make for great functional flexibility. Despite the progress made as far as invertebrates are concerned, the exact role of these neurons in the mammalian CPGs during swallowing or other activities is difficult to assess, and further experiments are now required to elucidate this point in the various CPGs.

The mechanisms that make it possible for the same neuron to participate in several sometimes antagonistic activities still remain to be determined. In invertebrates, the flexibility of the CPGs is conferred by the inputs,
which both restructure a CPG by changing the influences exerted on the synaptic connections between neurons and alter the intrinsic properties of the neurons composing the CPGs (82). It is worth noting that in the case of the NTS neurons, in vitro data on brain stem slice preparations have provided evidence that there is a cellular basis underlying the flexibility. The same NTS neuron can exhibit either tonic firing, burst firing, or a beating-like firing depending on the balance between excitatory and inhibitory inputs, which may modulate the interactions between several ionic conductances (Fig. 9A2) (162, 332, 333). If the same properties are preserved in vivo, it is possible that the role of each neuron is not in fact fixed once and for all. A neuron may function flexibly within a network and thereby participate in several behaviors (197). Whatever the case may be, the evidence available to date indicates that within the dorsal and ventral medulla, there exists a common pool of neurons that might have a multifunctional role. It can therefore be postulated that at least some of the components of the swallowing network are not dedicated to swallowing alone but can also serve some purpose in other central networks (Fig. 10C).

VI. CONCLUSION AND PROSPECTS

Swallowing is a vital motor activity that serves alimentary purposes and protects the upper airway. This complex motor sequence involves the coordinated and synchronized contraction of more than 25 pairs of muscles in the oropharynx, larynx, and esophagus, which are active during an all-or-none oropharyngeal phase, followed by the primary esophageal peristalsis. Swallowing is also a rhythmic motor event, at least as far as its oropharyngeal stage is concerned. Swallowing depends on a CPG located in the medulla oblongata, which involves several brain stem motor nuclei (V, VII, IX, X, XII) and two main groups of interneurons: a dorsal DSG in the NTS and a VSG located in the ventrolateral medulla above the nucleus ambiguous. Within the CPG, neurons in the DSG play the leading role in generating the swallowing pattern, while neurons in the VSG act as switching neurons, distributing the swallowing drive to the various motoneuronal pools. It is quite remarkable that a CPG for a fundamental motor activity should be located within a primary sensory nucleus, namely, the NTS. As in the case of other CPGs, the functioning of the central network can be influenced by both peripheral and central inputs, which serve in particular to adapt the swallowing drive to the size of the bolus to be swallowed.

Little is known so far about the mechanisms at work in the CPG. Among the various neurotransmitters that are known to intervene in swallowing, the EAA receptors, in particular those of the NMDA type, play an important role in triggering the motor event and patterning the motor sequence. The sequential burst firing of the swallowing neurons probably depends on the pattern of intrinsic connections within the swallowing network. Within this network, central inhibitory connections, in particular, play a major role, resulting in a rostrocaudal inhibition within the network which parallels the rostrocaudal anatomy of the swallowing tract and acts in such a way that when the neurons controlling the proximal parts of the tract are active, those which command more distal parts are inhibited. Intrinsic properties of the neurons, in particular those of NTS neurons, probably also contribute to determine the shaping and timing of the swallowing motor pattern. In particular, pacemaker-like properties of NTS neurons are also thought to greatly contribute to patterning the bursting neuronal firing and generating their oscillatory behavior during rhythmic swallowing. As clearly demonstrated in the case of invertebrate pattern generators, it now seems likely in the light of several recent results that the swallowing CPG may show some flexibility. These results suggest that at least some of the swallowing neurons may be multifunctional neurons and belong to pools of neurons that are common to several CPGs.

It will obviously be a long and difficult task to further increase our knowledge about the neuronal mechanisms involved in swallowing in mammals. Several possible lines of research can nevertheless be indicated as means of answering questions yet unsolved, using new approaches to the neurophysiology of swallowing. One of the most important questions that remains to be answered about the neural control of swallowing is whether the central nervous system of the species with a smooth muscle esophagus may include a network of neurons that is similar to that of the species with a striated esophagus, and if so, how this network functions. The supramedullary influences on swallowing, which have been only sparsely documented so far, require more thorough investigation. In particular, this would make it possible to specify the role of these central influences in several pathological situations. Interestingly, it is now possible in studies of this kind to use new approaches such as cortical evoked potential, transcranial magnetic stimulation, and magnetoencephalographic recordings, not only on experimental animals but also on humans (14, 15, 53, 119, 122, 339, 348). To further elucidate the working of the CPG, it will also be necessary to identify at the cellular level the action of neurotransmitters and neuromodulators and the types of receptors involved. This would provide valuable information about the possible sites of action for therapeutic agents. It seems to be quite impossible at present to definitely elucidate the intrinsic mechanisms underlying swallowing pattern generation in mammals. However, these basic mechanisms can be studied in networks consisting of limited populations of neurons, such as those with which invertebrates are endowed, or...
using computational approaches and modeling natural processes with artificial networks (116, 169, 240). Studies on other experimental models such as the isolated brain stem preparations may also be useful for this purpose (76, 264). However, depending on the in vitro preparation used, the developmental aspects, such as possible postnatal changes in the swallowing mechanisms, should not be overlooked. Interestingly, and somewhat paradoxically, some data have suggested that although swallowing is a vital function, the underlying mechanisms may be not fixed at birth (206, 229, 271, 272, 315, 357, 359). Finally, studies on complex pattern generators such as those operating in mammals will no doubt greatly benefit from the latest methodological approaches. In particular, it seems likely that by focusing research on whole populations of neurons rather than recordings single neurons, it will be possible to obtain new insights as to how the mammalian CPGs function. Multiple recordings based on electrophysiological and/or optical methods (92), and the use of sophisticated functional brain imaging techniques such as magnetic resonance imaging or positron emission tomography (93) already used in swallowing-related studies (120, 121), will undoubtedly throw new light on the neural control of swallowing and may give rise to new insights about the way in which the various neuronal networks in the mammalian nervous system work and interact.

I acknowledge the assistance of Caroline Brocal and Marianne Sellem for secretariat, that of Jocelyne Roman and Yvette Minguela in preparing the illustrations, and that of Jessica Blanc for revision of the English.

I take great pleasure in acknowledging my colleagues who have participated in different phases of the work on swallowing.

The author’s laboratory is mainly funded by the Ministère des Universités and the Center National de la Recherche Scientifique (ESA 6034). The support of the Institut National de la Recherche Agronomique (EA 1033) is gratefully acknowledged. Parts of the work on swallowing have also been supported by grants from the Institut National de la Santé et de la Recherche Médicale.

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