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Neural Mechanisms of Swallowing: Neurophysiological and Neurochemical Studies on Brain Stem Neurons in the Solitary Tract Region

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Abstract. Neurophysiological studies of the nuclei of the tractus solitarius (NTS) and adjacent regions have provided a partial understanding of the integrative brainstem network underlying swallowing and related functions such as respiration. The NTS is also richly endowed with an abundance of neuropeptides and other neuroactive substances, but only limited information is available on their influences on neurons involved specifically in swallowing. Since dysfunction of these neurophysiological and neurochemical regulatory mechanisms in the NTS region may be important in pathophysiological conditions such as dysphagia, increased awareness of and focus on these mechanisms are warranted. This paper outlines recent neurophysiological and neurochemical data that provide information on the afferent inputs and neurophysiological properties of neurons in NTS and adjacent caudal brainstem regions implicated in swallowing, respiration, and respiratory-related reflexes.

Key words: Swallowing – Neurons – Solitary tract – Neuropeptides – Regulation – Respiration.

Swallowing is a complex reflex event that reflects the synergistic bilateral activity of several muscles. Although this reflex is a "primitive" one in the sense of its manifestation in most animal species, the large number of muscles involved and the complex integration required between the alimentary and respiratory muscles result in this reflex being one of the most complex events even in higher animals. The alimentary function of swallowing has long been acknowledged by virtue of its vital role in ingestion, but it is now also recognized as a protective reflex of the airway [1–4]. This duality of reflex function (i.e., alimentary and respiratory) underlies the need for complex coordination and interplay between the various muscles involved.

Muscles innervated by several cranial nerves (e.g., V, VII, IX, X, XI, XII) participate in swallowing. In addition, muscles innervated by intercostal and phrenic motoneurons are involved and, in some cases in which additional bracing of the tongue base and mandible are needed (e.g., some patients with cerebral palsy), muscles supplied by the cervical motoneurons may also be recruited into action. The recruitment of additional muscles, abnormal muscle activity, or lack of coordination between muscles is reflected in several dysfunctional states of swallowing. These clinically manifested disturbances are in large part related to changes in the peripheral (i.e., sensory) inputs and central neural mechanisms normally involved in the appropriate coordination and orchestration of the swallow synergy. A growing body of evidence points to the likelihood that many dysphagic conditions could be a reflection of pathophysiological alterations in the neurophysiological mechanisms controlling swallowing and in the neurochemical processes that underlie these mechanisms. We shall consider here some of the neurophysiological and neurochemical substrates implicated in the initiation and regulation of the swallow synergy. We will focus especially on the role of the nuclei of the tractus solitarius (NTS) and adjacent brainstem regions in these processes, and integrate our own findings with those of others who have also provided important knowledge of the neural mechanisms underlying swallowing and related functions such as respiration.

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Our reason for focusing on the NTS relates to its vital role in the neural substrate of swallowing. Swallowing can be reflexly or volitionally initiated, and its reflex initiation can be produced by stimulation of peripheral regions particularly supplied by the glossopharyngeal (IX) nerve and superior laryngeal nerve (SLN), a branch of the vagus nerve. These reflex sensory inputs, as well as projections from higher brain centers involved in the volitional initiation of swallowing (e.g., cerebral cortex) have direct access to the NTS region. The NTS is a bilateral structure that constitutes an integral relay and integrative brainstem center intimately involved in autonomic control and in the regulation of visceral function [see for review 1, 2, 3, 5–7]. Thus, the NTS is involved not only in a variety of reflex functions of the upper alimentary and respiratory tracts including swallowing but also in such diverse functions as cardiovascular regulation, respiratory control, and taste. The NTS and its subadjacent region contain neurons that contribute to each of these various functions and, as reviewed in the Discussion (see below), recent research suggests that this region constitutes at least part of the neural substrate of the central pattern generator necessary for the initiation and orchestration of the swallow synergy. Many of the neurons in this region show physiological properties consistent with a role in swallowing and in the necessary coordination with other vital functions such as respiration. Moreover, recent research has also revealed that the NTS is a site of particular concentration of several neurochemical substances (e.g. amino acids, neuropeptides, biogenic amines) and a role for at least some of these has been demonstrated in the initiation and control of swallowing and related activities. Thus, in any consideration of the biological basis of swallowing and dysphagia, it is essential to examine the neurophysiological and neurochemical mechanisms operating in the NTS region.

The objective of our own experiments has therefore been to determine the chemical sensitivities of neurophysiologically identified single NTS neurons, in order to relate these to information on neural pathways containing specific chemical mediators of synaptic transmission as well as with the types of transmitter receptors located in the NTS. The experimental approach involved inserting a microelectrode into the vicinity of the NTS and recording the electrical activity of one single neuron at a time. This extracellular activity is manifested as neuronal action potentials, and the frequency of action potentials (i.e., the discharge rate) reflects the level of excitation of the neuron. Respiratory neurons were the focus of these investigations because they constitute an electrophysiologically identifiable group of neurons and they can be influenced physiologically by a number of maneuvers. In addition, however, other types of neurons in the vicinity of the NTS were also studied, including a population we have termed *reflex interneurons*. These neurons do not share the phasic spontaneous discharge that characterizes respiratory neurons, but they all do respond in a similar fashion to vagal (e.g., SLN) and IX sensory inputs and have been implicated as interneuronal elements in brainstem pathways underlying upper alimentary tract and respiratory reflexes such as swallowing [for review see 2, 8, 9].

Chemical mediators of synaptic transmission selected for study in our experiments were glutamate, γ-aminobutyric acid (GABA), serotonin (5-HT), as well as the peptides substance P, enkephalin, angiotensin II, vasopressin, and oxytocin. The rationale for this selection is presented in the Discussion section, along with further evidence implicating these neuroactive chemicals in NTS function. To study the chemical sensitivities of the single neurons, the technique of microintophoresis was used, in which small quantities of a selected chemical can be applied into the local vicinity of the neuron whose activity is being recorded. Thus, the micropharmacology of a neuron can be studied in situ.

Methods and Results

Only a brief description of the experimental approach will be given here. The interested reader is referred for more detail to previous publications [10–16].

Animal Preparation

Experiments were carried out on adult cats anesthetized with α-chloralose (60 mg/kg), i.v.) throughout the experiment. Femoral arterial pressure, percentage end-expired CO_2 concentration and rectal temperature were monitored continuously and maintained within normal physiological limits. Each animal was paralyzed with pancuronium bromide and ventilated artificially by a respiratory pump. The head was placed in a stereotaxic frame and the medulla exposed to allow the stereotaxic introduction of the electrode for neuronal recording and microiontophoresis in the vicinity of the right NTS. The left and right vagus and superior laryngeal nerves were exposed for subsequent electrical stimulation (0.1–5 mA, 0.1–2 ms, constant current).

Electrodes

Multibarreled micropipettes were used for neuronal recording. Seven glass capillary tubes were assembled and drawn out under heat to yield an overall diameter of the drawn end of 5–10 μm.

The central barrel was filled with 2.7 M NaCl, and was used for recording. Peripheral barrels could be filled with any combination of solutions of the chemicals listed above; thus, each chemical agent could be ejected by the application of a small DC current to the appropriate barrel.

Recording and Classification of Neurons

Neurons in histologically confirmed sites in the NTS were identified on the basis of their functional properties as being either respiratory neurons or presumed reflex interneurons. Respiratory neurons showed a spontaneous rhythmic discharge in synchrony with respiration (monitored by simultaneous recordings of phrenic nerve activity). The reflex interneurons showed no rhythmic activity but could be orthodromically excited at a short latency by vagal or SLN stimulation. In addition to these two major groups, other neurons were also recorded in the dorsal column nuclei dorsal to the NTS (these neurons responded at short latency to electrical and tactile stimulation of only the ipsilateral fore- or hindpaw) and in the reticular formation subjacent to the NTS (these neurons had widespread inputs and responded to electrical or tactile stimulation of tooth pulp, facial skin, and SLN). The effects of the chemical agents on these particular neurons are described elsewhere [11–14]. Recorded activity of a neuron was displayed on oscilloscopes (for observation and for photographing selected responses) and was also led through a gated mean frequency meter to a pen recorder that provided continuous display of the neuron's activity. The effects of the iontophoretically applied chemical agents were then assessed on the spontaneous or evoked activity of the neuron and each agent was applied at least twice to ensure that an observed effect of the agent on the neuron was reproducible.

In iontophoretic studies, in which the chemical sensitivities of the neurons were determined, an effect of an applied neuroactive agent was considered to be a genuine response if it was reversible in time, reproducible, and not mimicked by the ejection of Na^+ through another electrode barrel. When a response was observed, it was usually examined at various levels of current application to ensure that the magnitude of the response varied directly with the amount of current applied. Due to the stringent criteria we applied to consider an effect a genuine response, and to the variable nature of the activity of most central neurons, more neurons were tested with each neuroactive agent than are reported. Only those neurons considered to yield unequivocal results, including those considered to be unaffected by the agents, are included in this report. With the exception of one expiratory neuron that was excited by glutamate, all respiratory neurons fired in phase with phrenic nerve discharge and were therefore classified as inspiratory.

General Characteristics of Neurons

Respiratory neurons exhibited a spontaneous rhythmic discharge of action potentials in phase with phrenic nerve activity (10–20/min), and thus these neurons were classified as inspiratory neurons. This rhythmic discharge continued when the pump was briefly turned off, demonstrating that the rhythmicity originated from within the brainstem rather than from sensory afferents. However, an afferent input to some of the neurons was indicated by their excitatory response to sensory stimulation; most neurons were excited by vagal and/or SLN stimulation, at minimum response latencies of 3–6 ms. These orthodromically evoked responses did not follow vagal or SLN stimulation rates greater than 10 Hz. In fact, the rhythmic activity of these respiratory neurons and the phrenic nerve could be depressed by SLN stimulation at 10 Hz; this depression is probably related to the apnea that characteristically occurs during swallowing elicited, for example, by such SLN stimulation.

Neurons classified as *reflex interneurons* were found interspersed in the NTS among respiratory neurons. These interneurons showed no rhythmic respiratory-related activity but could be excited by vagal and/or SLN stimulation, with minimum response latencies in the 3–6 ms range. Approximately one-third of these neurons exhibited spontaneous discharge, but this activity was unrelated to phrenic nerve activity.

Characteristics of Response to Glutamate

Glutamate generally had an excitatory effect on neurons in the vicinity of the NTS [11], characteristic of its actions on neurons throughout the central nervous system [17]. Excitation consisted, typically, of a rather abrupt increase in activity in response to application of 1–30 nA of negative current through the barrel containing glutamate. The onset of the excitatory response occurred within 1–2 s of current onset, excitation persisted throughout the period of application, and the response ended within 1 s of the end of current application. In the case of neurons responding to electrical or mechanical stimulation of sensory inputs (e.g., SLN), glutamate also increased the probability of the appearance of an evoked response and tended to decrease the latency of the first evoked action potential. The magnitude of the response varied directly with the amount of ejecting current and was approximately the same to each of a succession of similar applications.

Respiratory neurons, we were interested to discover, provided the exception to this generality. In addition to those excited by glutamate, about half of the respiratory neurons were unaffected by glutamate application or were relatively insensitive. Thus, we documented 32 glutamate-sensitive respiratory neurons that were excited by 1–30 nA of current, while another 26 respiratory neurons were glutamate-insensitive since they could not be excited. Excitation consisted of an increase in the number of action potentials per respiratory burst, usually due more to a prolongation of the burst than to an increase in the frequency within the burst. Only occasionally could a respiratory neuron be driven to fire throughout the respiratory

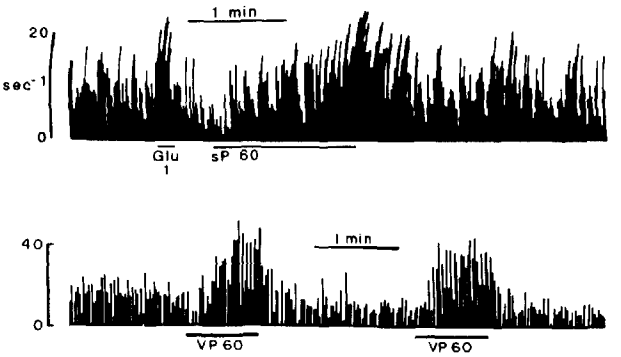

Fig. 1. Rate meter records from two neurons recorded from the nuclei of the tractus solitarius. *Upper record* shows effects on a single reflex interneuron of iontophoretic application of glutamate (*G*) with 1 nA of current and similar application of substance P (sP) using 60 nA. Note the different time course in the effects of the two agents. *Lower record* shows the effects on a single respiratory neuron of iontophoretic application of vasopressin (VP) with 60 nA. Note the reproducibility of this response with repeated application of vasopressin.

cycle; that is, the period of depression in the cycle usually could not be fully overcome.

Reflex interneurons were almost all excited by glutamate (23 of 25 tested) (Fig. 1). Currents used were 1–60 nA, and there was no clear division into two groups as described above for respiratory neurons. Table 1 summarizes these effects.

Characteristics of Response to GABA

GABA depressed all NTS neurons tested, including 19 respiratory neurons and 11 reflex interneurons. These neurons were particularly sensitive to GABA, most being clearly depressed with 1–15 nA of current (maximum current required was 45 nA). Responses were also rapid, with onset times of less than 1 s. Responses typically reached a maximum depression in 1–2 s and returned to preapplication levels within 1–2 s after the current was switched off.

Characteristics of Response to Serotonin

Typical of its effects elsewhere in the central nervous system, serotonin had variable effects on neurons in the NTS [15]. Currents of 25–100 nA were used to eject serotonin. Of the respiratory neurons tested thoroughly, 15 were excited, 2 were depressed, and 9 were unaffected. Excitation was typically slower than the responses to amino acids and consisted of an increase in the number of action potentials for each respiratory burst. This increase started within 20 s of the onset of current application and continued to grow in magnitude throughout the application. When the current was terminated, the number of action potentials per burst usually decreased slowly, returning to preapplication levels over the next 30–60 s. The depressant responses were also relatively slow.

Of the 8 reflex interneurons tested, none were excited, 4 were depressed, and the remaining 4 were unaffected. Depression consisted of a decrease in spontaneous activity and/or a decrease in the probability of a spike response to electrical stimulation of the vagus or SLN. The time course of the depression was roughly parallel to that observed with respiratory neurons.

Characteristics of Response to Substance P

Substance P had slow excitatory effects on neurons in the NTS [11] that resembled the excitatory responses observed on single neurons in other structures of the central nervous system. In the case of NTS neurons, currents of 15–120 nA were customarily used. Of 27 respiratory neurons studied with substance P or with a structural homologue with similar effects – eledoisin-related peptide – 17 were excited; depression was never observed in response to the application of substance P. The response began in 15–30 s and consisted of an increase in the number of action potentials in the respiratory burst. In some cases this appeared to be due mainly to an increase in the duration of the burst, while in others it appeared to be due to an increase in the frequency of action potentials in the burst. Throughout the current application period the excitation increased. When the current was stopped a slow return of the activity to preapplication levels was observed over the following 60–90 s. Excitation also consisted of an increase in the probability of evoked responses to electrical stimulation of the vagus or SLN.

Of the 9 reflex interneurons tested, 8 were excited. Excitation consisted of an increase in the probability of the appearance of an evoked spike and/or an increase in the frequency of discharge. The time course of the excitation resembled that of respiratory neurons.

Characteristics of Response to Enkephalin

Clear results were obtained from 20 respiratory neurons. Following application of currents of 16–80 nA, depressed responses were seen with 9 neurons; no effects were seen with the remaining neurons. This response was very slow and prolonged, even in comparison with the response to substance P. In 4 cases, the response to enkephalin was tested with the μ-opiate receptor antagonist, naloxone, which produced partial or complete reversal of the response to iontophoretic application of enkephalin [15].

Of the 5 reflex interneurons tested thoroughly 4 were depressed and the remaining neuron was unaffected. The time course of the response was similar to that described for respiratory neurons.

Characteristics of Response to Angiotensin II

Eight of 27 respiratory neurons were excited by angiotensin II (currents were 30–100 nA) and none were depressed. The response consisted of a slow increase in activity, similar to that observed with substance P.

Reflex interneurons were excited in a similar manner; of the 8 tested, 5 were excited [16].

Characteristics of Responses to Vasopressin and Oxytocin

Approximately half of the respiratory neurons tested with 30–60 nA of vasopressin ($N = 21$) and/or oxytocin ($N = 16$) were excited. This effect was slow in onset and prolonged in duration. In some cases the excitation was great enough to induce phase-spanning in respiratory neurons [12].

The reflex interneurons that were excited (4 of 6 tested with vasopressin; oxytocin was not tested) exhibited a somewhat slower response, which typically reached its peak about 30 s after the end of application and required up to 2 min for full recovery.

Discussion

Physiological Mechanisms

Swallowing depends on a brainstem neural substrate that integrates peripheral sensory inputs and central neural influences and produces the sequential, all-or-none pattern of excitation and inhibition manifested in the various groups of motoneurons that supply the muscles participating in this complex sensorimotor reflex. By virtue of its receipt of afferent inputs from several cranial nerves and central neural structures and the organization and central connections of its neurons, the NTS plays an integral role in producing the swallow synergy.

Peripheral Afferent Inputs Triggering Swallowing. In most animals including humans, swallowing can

Table 1. Summary of predominant effects (*) of neuroactive agents on single neurones in the NTS

Neuroactive Agent	Neuron Type	Excitation	Depression	References
Glutamate	Reflex interneuron	*		11
	Respiratory neuron	*		11, 56
GABA	Reflex interneuron		*	this manuscript; 86
	Respiratory neuron		*	this manuscript; 87, 88
Serotonin	Reflex interneuron		*	15
	Respiratory neuron	*		15
Substance P	Reflex interneuron	*		11
	Respiratory neuron	*		11
Enkephalin	Reflex interneuron		*	15
	Respiratory neuron		*	15, 100
Angiotensin II	Reflex interneuron	*		16
	Respiratory neuron	*		16
Vasopressin, oxytocin	Reflex interneuron	*		12
	Respiratory neuron	*		12
Acetylcholine	Respiratory neuron	*		114, 134, 137
Catecholamines	Respiratory neuron		*	112
Purines				
ATP	Respiratory neuron	*		146
adenosine	Respiratory neuron		*	146
Somatostatin	Respiratory neuron		*	82
TRH	Respiratory neuron	*		149

be most readily elicited from the pharynx and larynx. Cranial nerves IX and X are particularly involved in innervating these peripheral regions. Tactile stimuli excite pharyngeal and laryngeal receptors and elicit swallowing, and in the epiglottic part of the larynx, which is supplied by the SLN, water is a particularly effective stimulus [e.g., 4, 18–23]. Group II and III primary afferents in the SLN and IX nerve appear to be primarily responsible for supplying these mechanoreceptors and chemoreceptors and conducting their messages into the brainstem. Recent studies have also identified several neurochemical substances in some IX and X afferents, their cell bodies, and the tissues they supply [for review, see 24–26]. Although there does not yet appear to be any correlation of a particular substance or substances with particular afferents involved in swallowing, it would seem highly likely that afferents specifically involved in triggering swallowing contain one or more of these neurochemicals. A wide range of neuroactive substances has been described, and include several biogenic amines and catecholamines (e.g., 5-HT, dopamine, norepinephrine), acetylcholine, and neuropeptides (e.g., substance P, enkephalin). Substance P is found, for example, in cell bodies in the nodose and jugular ganglia as well as in nerve fibers in the upper respiratory and upper alimentary tracts, and its distribution in the NTS is markedly decreased after vagal or IX nerve section, indicating its peripheral origin [e.g., see 24–27]. The presence of some of these substances in primary afferents and in primary afferent terminals in the NTS suggests a role for them in synaptic transmission or modulation within NTS, and might be related to our findings of, for example, excitatory effects of substance P on reflex interneurons as well as respiratory neurons within the NTS that can be excited by short-latency inputs from the SLN and vagus nerve.

In many animal experiments, for expediency, electrical stimulation of afferents of cranial nerves IX and X has been used to elicit swallowing. Swallowing can be readily elicited by stimulating the SLN branch of the vagus. A particular feature of these SLN-induced swallows is the 10–30 Hz optimal stimulation frequency, which corresponds to the optimal tuning of NTS neurons driven by pharyngeal mechanical stimuli [28; for review, see 1–3]. These SLN stimulation parameters are also optimal for producing a simultaneous and powerful cessation of respiration that normally is a necessary and invariant accompaniment of swallowing and that, it is interesting to note, may be particularly prolonged and in some cases irreversible in neonatal animals [see 2, 9]. This apneic response

was reflected in the present study in the suppression of rhythmic activity in the phrenic nerve and NTS respiratory neurons that could be induced by 10 Hz SLN stimulation. Only limited information is available about the neurochemical mechanisms contributing to suppressive effects such as these on respiration, as well as to the excitatory events triggering swallow (see section on Neurochemical Mechanisms).

Brainstem Mechanisms. Some anatomical studies and brainstem lesioning experiments have indicated that the brainstem integration of swallowing primarily involves the pontine or rostral medullary reticular formation [e.g., 29–31], while other studies suggest that the NTS and subjacent caudal medullary reticular formation are involved [8, 32, 33]. However, the anatomical documentation of projections from an area of the reticular formation or NTS to several cranial nerve motor nuclei involved in swallowing does not a priori implicate this particular region in swallowing per se, since these motoneuron pools are involved in numerous other muscle synergies (e.g., mastication, coughing, gagging, licking). Moreover, results of surgical lesion experiments are difficult to interpret since the lesions can have nonspecific actions and damage axons coming from or going to other areas of the CNS [see 2].

Electrophysiological experiments involving single neuron recordings in the brainstem have provided more definitive evidence that at least the NTS and its adjacent regions are elements of the integrative brainstem network involved in swallowing. Some authors have referred to this network as the "swallow center" but, in view of its likely diffuseness, it might be better viewed as a central pattern generator. The precise functional organization of this central pattern generator is still unclear [e.g. 3, 8, 34], but electrophysiological studies in the last 15 years have provided some insights, at least as far as NTS and subjacent regions are concerned. As noted above, the NTS is the termination site of IX and X afferents involved in swallowing [for review, see 2, 35–37], and stimulation of this region as well as IX and SLN afferents can elicit swallowing. Neurons in and adjacent to NTS can be excited by IX and SLN stimulation at latencies consistent with the receipt by many of them of monosynaptic IX and SLN inputs [8, 13, 28, 33, 38–40]. In the present studies, we also documented that many NTS neurons could be excited by SLN stimulation at latencies consistent with a monosynaptic or disynaptic input. These neurons also receive inputs from higher brain centers such as the cerebral cortex, stimulation of which can evoke swallowing [e.g. 31, 39, 41, 42]. The pioneering work of Roman, Jean, and their colleagues in Marseille have shown that many of these NTS neurons are active during swallowing [8, 33, 39, 43]. The retention of such activity patterns in many of these neurons during muscle paralysis (to eliminate sensory feedback) suggests that their discharge patterns can be independent of sensory input and may represent intrinsic neural activity involved in the drive to the various motoneurons active during swallowing. Three major patterns of neuronal activity have been documented (early, late, very late) depending on their temporal relation to the muscle activities of the different phases of swallowing (oral, pharyngeal, oesophageal). Jean and colleagues have reported that these neurons represent a neuronal group they have termed the *dorsal medullary swallowing neurons*; by anatomically and electrophysiologically defined connections, these neurons project to more ventral neurons near the nucleus ambiguus, which these workers refer to as the ventral medullary swallowing neurons. Although both groups are considered to be integral components of the swallow central pattern generator, the ventral group in particular may have projections to the cranial nerve motoneuron pools. This supports the view that they may be command interneurons or premotor neurons for motoneurons involved in swallowing.

Peripheral Modulation. It is generally considered that swallowing is relatively insensitive to sensory feedback and that once it is triggered, it will go through to completion with little peripherally induced modification of its muscle activity patterns. However, it is now clear that under certain conditions the muscle activities can be modified during swallowing. For example, the rate of swallowing or the muscle activity patterns during swallowing can be altered by peripheral disturbances, differences in bolus form and consistency, and presence or absence of saliva, and such sensitivity of the swallow synergy may have implications in pathophysiological conditions affecting the alimentary and respiratory tract and in the training or relearning of swallowing in clinical situations [see 2, 3, 34]. In electrophysiological studies of NTS and adjacent regions, it has also been found that stimulation of V afferents and especially IX and SLN afferents can exert facilitatory or inhibitory influences on the responses of neurons in these regions to upper respiratory and alimentary tract excitatory inputs [28, 38, 40]. Swallowing can also be modulated by these IX and SLN inputs, as well as

by V inputs, for example, from lingual nerve and periodontal receptors [2, 3]. The facilitation of swallowing demonstrated in some of these studies by simultaneous stimulation of several afferent inputs suggests ploys that might be adopted clinically in the treatment of some dysphagic problems.

The inhibitory effects of IX and SLN afferent stimulation on these neurons appear to involve presynaptic inhibitory mechanisms, although postsynaptic inhibitory mechanisms also probably contribute [e.g., 44, 45]. In agreement with earlier findings [e.g. see 13], we noted in the present study that SLN stimulation at 10 Hz could also produce a powerful inhibition of the rhythmic activity of most respiratory neurons. This is consistent with the observations that SLN stimulation can induce an associated depression of phrenic nerve activity; the apnea (see above) produced is a necessary accompaniment of swallowing to assist in the protection of the airway. Thus, the inhibitory changes in activity that are a feature of the respiratory muscles, as well as the inhibitory phases that are seen immediately preceding or during a swallow in many other deglutitory muscles [e.g., see 2, 3, 46], may be a reflection of these inhibitory effects that occur on neurons in the NTS region. Several of the neurochemicals outlined below (see section on Neurochemical Mechanisms) would be potential candidates for the neurotransmitters or neuromodulators involved in these complex inhibitory interactions.

The sequence of closely linked and closely timed excitation and inhibition ensure the coordinated and synergistic muscle activity patterns that provide for efficient transit of the bolus and protection of the airway. The occurrence of inhibition may also filter out certain reflex effects that might otherwise disrupt this orchestrated synergy [34, 46]. Support for this view comes from findings that peripherally evoked responses in some NTS neurons [33] and V brainstem neurons [34] are depressed during swallowing, and that certain reflex behaviors and central neuronal responsiveness are depressed during other programmed motor behaviors such as mastication [47]. Alterations in neurophysiological and neurochemical mechanisms underlying these important modulatory influences may explain, at least in part, the swallowing difficulties that occur in a number of central neural dysfunctional states. As the next sections point out, these pathophysiological conditions may also involve changes in modulatory influences and neurochemical mechanisms related to higher brain center inputs to NTS.

Central Neural Modulation. A number of cerebral cortical and subcortical sites project directly or indirectly to NTS, and their stimulation can initiate or modify swallowing [for review, see 1–3, 8, 46]. As noted above, these inputs to NTS have clinical significance since deficits in swallowing and feeding behavior can result from dysfunction of these higher brain centers, such as in stroke, cerebral palsy, or parkinsonism [3, 48–50]. Stimulation of certain regions of the cerebral cortex can initiate or facilitate the triggering of swallowing, and the documented cortically induced excitation of NTS neurons is a likely mechanism effecting this behavior [e.g., 3, 31, 39, 41, 42]. Swallowing can also be modulated by subcortical sites especially centered in the hypothalamus, basal ganglia, limbic forebrain, periaqueductal gray, and cerebellum [e.g., 14, 31, 41, 51]. A pathway from the basal forebrain and involving the amydala facilitates swallowing and may involve the neurochemical dopamine [41, 51]. Periaqueductal gray stimulation, on the other hand, can suppress swallowing (and coughing) as well as NTS reflex interneurons; the reversal of the suppression by the opiate antagonist naloxone suggests that endogenous opioids may be involved in these particular modulatory influences on swallowing [14]. Catecholaminergic and serotonergic mechanisms have also been implicated in some of these central neural modulatory influences, and the following section outlines in more detail the neurochemical mechanisms that underlie the regulation of NTS neurons and swallowing, and how our present findings relate to these mechanisms.

Neurochemical Mechanisms

A general conclusion that may be derived from our studies on the chemical sensitivities of NTS neurons is that at least for a number of putative chemical mediators of synaptic transmission, specific responses can be elicited from NTS neurons by close application of these chemicals into the local vicinity of the neuron (Table 1). It is inviting to speculate, then, that each of the chemicals so implicated is therefore a neurotransmitter. However, before this latter conclusion can justifiably be drawn, it should be pointed out that neuroscientists have come to accept that an effect or action on a neuron is only one of a number of criteria that must be satisfied before such a conclusion can be made with confidence.

What follows is an outline of these criteria, followed by the available evidence on the principal chemical mediators that has accumulated to sup-

port the possible roles of these chemicals as a mediators of synaptic transmission in the NTS. These chemicals will be listed in the following order: those implicated as mediators of synaptic transmission from primary afferent neurons conducting information to the central nervous system (glutamate, substance P, calcitonin gene-related peptide, and somatostatin), those implicated in transmission from local interneurons in or near the NTS (GABA, enkephalin, serotonin, and catecholamines) and chemicals acting as mediators from fibers projecting to the NTS from distant structures within the central nervous system (vasopressin, oxytocin, angiotensin II, acetylcholine). It will be apparent from this survey that despite a reasonable amount of evidence implicating these chemicals in synaptic transmission in the NTS, little direct evidence has been obtained linking them specifically in swallowing.

Criteria for Chemical Transmission. A synaptic transmitter should be located in the presynaptic nerve terminal, mechanisms for its synthesis should be present in its cell body, its release should occur in conditions known to activate the synapse, when applied exogenously it should mimic in the postsynaptic cell the effects of activation of the synapse, both the synaptic response and the responses to exogenously applied chemical should be blocked in a similar fashion by a selective antagonist, and, finally, mechanisms should exist in the region of the synapse to inactivate the chemical (so that its effect is limited in time) and to remove it or its metabolic products from the region of the synapse. Further details may be found in work by Werman [53] and McLennan [54].

Glutamate. Glutamate is one of the most ubiquitous neurotransmitters in the mammalian central nervous system [17] and particularly high concentrations are found in the NTS [54, 55]. The fact that the concentration of glutamate in the NTS is markedly reduced after removal of the nodose ganglion or after section of cranial nerves IX and X [54, 55] further suggests that its presence in the NTS is in primary afferent nerve terminals. Although glutamate has not been directly implicated in swallowing, our electrophysiological studies on NTS neurons indicate that its typically rapid and brief effects on reflex interneurons and respiratory neurons are consistent with a possible role as a fast-acting transmitter [11, 56]. Its release has been observed in the NTS in response to electrical stimulation of the vagus nerve [57] and an uptake mechanism, to remove it from the synapse, exists in the NTS [58].

Its functional role has been tied to baroreceptor inputs to the NTS [59]. However, microinjection of small quantities of glutamate or of glutamate-like agents into the NTS produces changes not only in cardiovascular parameters [55, 60] but also in respiration [60] and induces swallowing [61]. Similar microinjection of glutamate antagonists produces generally opposite effects to those of glutamate [62, 63].

Substance P. Of the peptides implicated in NTS function, this is the best documented. It is found in abundant quantities in the NTS, particularly in nerve terminals [64–66], including terminals of small-diameter vagal and IX afferents [27, 37]. Our report of excitatory effects of substance P on NTS reflex and respiratory neurons [11] and that of Morin-Surin et al. [67] demonstrated a delayed, slow, and prolonged excitatory response; the time course of this response is so different from the fast excitatory responses to glutamate that it seems likely that the peptide is serving a relatively slow function in synaptic transmission, possibly as a regulator of the efficacy of the synapse, analogous to the role proposed for substance P in primary afferent transmission of pain (nociceptive) afferents to the spinal cord [10] and brainstem [68]. Substance P appears to have specific receptors in the NTS [69] and although its microinjection has no effect on heart rate or arterial pressure, it does have a profound modulatory effect on respiration [70, 71]. It is interesting that substance P release has been detected in the NTS during hypoxia [72] and relatively high levels of substance P have been detected in brainstems of victims of sudden infant death syndrome [73].

Calcitonin Gene-Related Peptide. Calcitonin gene-related peptide (CGRP) is broadly represented in primary afferent fibres [74] and, in the NTS, is found in both cell bodies and nerve terminals [75]. It is found in all substance-P-containing primary afferents, but also afferents that do not contain substance P [74]. Some CGRP receptors are in the NTS [76]. It interacts with catecholamines in the NTS [77], and microinjection of a related peptide, calcitonin, into the rostral part of the NTS produces anorexia [78].

Somatostatin. Somatostatin, or somatotropin release-inhibiting factor (SRIF), has also been implicated in transmission from primary afferent fibers. Immunohistochemical studies have demonstrated

somatostatin in primary afferent nerve terminals in the NTS [79, 80] and binding studies have demonstrated somatostatin receptors in the NTS [81]. Somatostatin depresses respiratory neurons, perhaps through an interaction with a cholinergic mechanism [82]. Although microinjection of somatostatin into the NTS induces apnea [79] and changes in arterial pressure [83], its effects on swallowing or related reflex interneurons remain to be determined.

GABA. Gamma-aminobutyric acid (GABA) is an inhibitory amino acid with a widespread distribution in the mammalian central nervous system [17]. GABA and the GABA-synthesizing enzyme, glutamic acid decarboxylase, are present in a population of NTS neurons [58, 84, 85], consistent with a role of GABAergic neurons as local inhibitory interneurons. A GABA uptake mechanism has also been reported in the NTS [58].

NTS neurons are inhibited by local application of GABA [86]. Denavit-Saubie and Champagnat [87] have shown a depressant effect of GABA on brainstem respiratory neurons and a block of some of the periodic inhibitory input to these neurons by iontophoretic application of bicuculline [88]. Our electrophysiological data are consistent with these findings, except that we have shown its inhibitory effects specifically on presumed reflex interneurons and respiratory neurons in the NTS. Microinjection of GABA into the NTS produces a number of effects, including respiratory depression [89], increased arterial pressure [90], and inhibition of the baroreflex [63, 91]. It has been proposed that GABA mediates the inhibitory effects on respiration and vegetative reflexes of muscle afferent fibers [92], as well as inhibitory hypothalamic inputs to NTS neurons [93].

Opioid Peptides. Morphine-induced respiratory depression has been a well-known side effect since this drug came into use. The discovery in 1973 of opiate receptors and the subsequent discovery of endogenous peptides with opioid properties provide an understanding of the mechanisms of this effect of morphine on respiration. Each of the three families of opioid peptides, the enkephalins and those derived from dynorphin and β-endorphin, have been implicated in NTS function. For example, the presence in the NTS of neurons containing enkephalin [94] as well as the precursor to enkephalin [95] and the presence of nerve terminals containing enkephalin [79] implicate this type of neuron as a local inhibitory interneuron. Several types of opiate receptor have been found in the NTS [96, 97]. In studies in which selective activation of these different types of receptor has been done, the varied nature of the effects that we and others have documented on respiratory neurons [15, 98, 99] and reflex interneurons [15] in the NTS, and that others have seen on respiration [100, 101], suggests a rather specific type of regulation expressed by each of the different types of opioid peptide.

The precise function of opioid peptide-containing neurons in the NTS remains to be clearly identified, but they have been implicated in inputs to NTS neurons from sites in the periaqueductal gray and raphe regions [14]. They have been shown to produce an inhibition of respiration and related reflexes such as tongue protrusion, jaw opening, coughing, and swallowing that are in some cases reversible by naloxone [14]. As well as the well-known effects of opiate receptor activation on respiration, other functions appear to be regulated by opioid peptides in the NTS, including cardiovascular function [102] and baroreceptor reflexes [91].

Serotonin. Serotonin, also called 5-hydroxytryptamine (5-HT), is uniquely localized to a group of nuclei, the raphe nuclei, in the midline of the brainstem [103]. Nerve terminals from these nuclei are, however, widely distributed throughout the central nervous system, and serotonin is therefore involved extensively in regulation of central nervous function. Our electrophysiological data indicating a generally excitatory effect of serotonin on respiratory neurons and an inhibitory effect on reflex interneurons in the NTS [15] are consistent with an involvement of serotonin in the control of respiration and respiratory reflexes [70, 104]. Changes in respiration and respiratory reflexes are produced by administration of serotonin agonists to the NTS [105, 106], and inhibition of serotonin breakdown potentiates the respiratory effect of serotonin [106]. Serotonin-containing nerve terminals are found throughout the NTS [66], as are receptors for serotonin [107]. It is not surprising, therefore, that serotonin has been found to alter other functions as well.

The precise role of serotonin in swallowing is contested. While its administration into the fourth ventricle induces swallowing [108], microinjection into the region of the NTS inhibits reflex swallowing by electrical stimulation of the SLN [109, 110]. On the one hand it has been argued that the excitatory effects are likely to be nonspecific [61], while electrical stimulation of brainstem nuclei containing serotoninergic neurons inhibits reflex swallowing [14, 110].

Catecholamines. This family of neuroactive agents includes norepinephrine, epinephrine, and dopamine. The NTS is recognized as one of the brain nuclei containing neurons synthesizing norepinephrine [103], and these neurons, because of the length of their axons, function primarily as projection neurons from the NTS to other regions of the central nervous system. There is reason to believe, however, that NTS neurons may also be under the control of catecholamines in terminals of NTS neurons or neurons in other brainstem structures. Release of catecholamines has been detected from the NTS in vitro [111], and α_1- and α_2-adrenergic receptor types are located on neurons in the NTS [112], including α_2-receptors on presynaptic elements [113]. Terminals containing catecholamines are found in the NTS [84]. Catecholamines and their agonists have a predominantly depressant effect on brainstem respiratory neurons [114] and potentiate inputs to NTS from other regions [115]. Microinjection of catecholamines into the NTS produces changes in respiration [114], gastric motility [116] and cardiovascular parameters [117, 118]. In experiments on the effects of catecholamines on rhythmic swallowing elicited by stimulation of the SLN, an inhibitory effect was produced by microinjection into the NTS of norepinephrine and the α-adrenergic agonist, clonidine, as well as by microinjection of dopamine and its agonist, apomorphine [110]. In fact, it has been suggested that catecholamine effects are mediated possibly by a presynaptic action [119].

Vasopressin and Oxytocin. In view of the origin of these two neuroactive peptides in adjacent regions of the hypothalamus [24, 120, 121], and the similarity of their effects on central neurons, they will be considered together here. Radioimmunoassay and immunocytochemical techniques have demonstrated that vasopressin and oxytocin-containing cell bodies in the paraventricular nucleus of the hypothalamus project to NTS [120, 121] and vasopressin- and oxytocin-binding sites and terminals occur in NTS [122]. Our studies have indicated an excitatory effect on reflex interneurons and respiratory neurons in the NTS [12]. Thus, descending vasopressin- and oxytocin-containing fibers may mediate excitatory inputs from the hypothalamus to NTS reflexes. In fact, cardiovascular changes have been documented after vasopressin or oxytocin was injected directly into NTS [123, 124]. Pretreatment of the animal with a vasopressin antagonist abolishes the pressor response elicited by subsequent vasopressin injection into NTS [123], and the application of antagonist directly into NTS decreases the response to electrical stimulation of the paraventricular nucleus [125].

Angiotensin II. Best known for its peripheral effects, angiotensin II has recently come to be recognized as also having central nervous effects, most likely as a chemical mediator of synaptic transmission. Angiotensin II immunoreactivity [24] and degrading enzyme [126] are prevalent in the NTS. Binding sites [127] are also found in this region, perhaps on the terminals of primary afferents from the vagus nerve [128]. In addition to our electrophysiological study demonstrating an excitatory effect of angiotensin II on neurons associated with respiration and alimentary tract reflexes [16], microinjection studies have also demonstrated pressor effects [129] and depression of baroreflexes [130]. Intracisternal administration of angiotensin II induces emesis [131], although the precise site of action in this case is unknown.

Acetylcholine. Acetylcholine is perhaps best known for its role in neuromuscular transmission and in synaptic transmission in the autonomic nervous system. However, it is also generally considered to be an important mediator of synaptic transmission in the central nervous system [17], including in the NTS where one can observe an acetylcholine-synthesizing enzyme [132] as well as muscarinic receptors [133]. Effects of acetylcholine and related chemicals applied by iontophoresis to medullary respiratory neurons [114, 134] or microinjected into the NTS [135, 136] have been variable, possibly due to the use of anesthetics that alter the responsiveness of NTS neurons to acetylcholine [137; personal observations, 1989].

Purines. Adenosine-5′-triphosphate (ATP) was first implicated in sensory transmission in 1954 [138], but has received little further attention until recently, when a synaptically mediated sensory input to spinal sensory neurons was attributed to ATP and its metabolic product, adenosine [139–141]. Although purines influence respiration [142, 143] by an effect within the central nervous system [144], only recently has the NTS been implicated in these effects. Adenosine uptake sites are found in the NTS [145]. Moreover, we have recently observed excitatory and biphasic effects of ATP and depressant effects of the adenosine precursor, AMP, when applied to NTS respiratory neurons [146]. Microinjection of an adenosine analogue into the NTS depresses respiratory rate with a concomitant increase in tidal volume [147, 148].

Other Neuroactive Agents. Many other neuroactive agents are found in the NTS. Recent reviews listing these agents include those by Kalia et al. [19], Kalia [37], Leslie [24], Eldridge and Millhorn [104], and Mueller et al. [70]. Of the large number of such agents for which relatively little is known, some have, nonetheless, been implicated in regulation of specific functions in the NTS. Thus, to cite a few, thyrotropin-releasing hormone (TRH) has been shown to alter the activity of brainstem respiratory neurons [149] and, upon microinjection, produces changes in respiration [150, 151]. Its origin seems to be in neurons projecting to the NTS from raphe nuclei [152]. Neurotensin is found in cell bodies of the NTS [153] and therefore probably plays a role in local regulation within the NTS. It produces respiratory stimulation [154] or apneustic breathing [155] as well as anorexia [78]. Bombesin, which has otherwise been implicated in primary afferent transmisson [156], also produces respiratory stimulation [157, 158] and anorexia [78]. Atrial natriuretic factor (ANF), which is found in the NTS [159], as are receptors for ANF [160, 161], elicits changes in cardiovascular parameters when administered to the NTS [162].

Concluding Remarks

Several obvious conclusions may be drawn from this review. Most painful, perhaps, is the gross lack of detailed information on the roles of neuroactive chemicals in NTS function. Thus, the role of nearly all these neuroactive chemicals in swallowing per se is equally unclear and virtually unexplored. Our data indicating modulatory effects on NTS reflex interneurons (as well as respiratory neurons) presumed to serve in swallowing and related reflexes suggest that these chemicals may have important functions in regulating the central neural mechanisms underlying swallowing. However, considerably more information is required, especially on neurons specifically identified in mechanisms of swallowing. As in other areas of study, our understanding of dysfunction is also highly contingent on finding a suitable animal model to explore experimentally. It is certain that the control mechanisms in the NTS are complex, even if this conclusion is arrived at only on the basis of the number of chemicals in these nuclei. All the evidence indicates that this region of the brainstem is endowed with an unusual abundance of such chemicals.

Another obvious conclusion is that the control mechanisms must also be extensive in their governing of the sensory information arriving at the NTS. This can be assumed because of the wide range of effects that may be observed when the NTS is stimulated, either electrically or chemically. Such diverse physiological functions as arterial pressure, respiration, swallowing, emesis, and gastric motility have been implicated. Of course, these functions are linked by the coordination required for day-to-day control. It is clear, then, that a certain apparent overlap in the chemical basis of control of these various physiological functions is perhaps the most efficient way of governing these functions. Moreover, dysfunction of these neurochemical/neurophysiological regulatory mechanisms in the NTS region may be important in pathophysiological conditions such as dysphagia. There is an urgent need for an increased research focus on neural mechanisms within the NTS and adjacent regions to clarify the processes underlying swallowing and pathophysiological disturbances of swallowing.

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