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Swallow Remodeling of Respiratory Neural Networks

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Abstract

Swallow is defined as the coordinated neuromuscular activity of the mouth, pharynx, larynx and esophagus. Movement of a bolus and air must be coordinated by swallow remodeling of respiratory pattern. The brainstem contains respiratory and swallow neural control networks that generate the pattern for breathing and swallow. Swallow control of respiration is proposed to be through recruitment of swallow neural elements that retask existing respiratory neural network elements. Swallow reconfiguration of the respiratory neural network is fundamental to airway protection and integrated with other airway protective reflexes. Thus, swallow, breathing, cough, and other airway defensive behaviors are produced by a central neural motor system that share elements. It is hypothesized that swallow and airway defensive behaviors are controlled by a recruited behavioral control assembly (BCA) system that is organized in a fashion that allows for precise coordination of the expression of these behaviors to maintain airway protection.

Swallow and breathing share a common anatomical pathway in the pharynx. Swallow is classically defined as a coordinated neuromuscular activity of the mouth, pharynx, larynx, and esophagus to allow passage of ingested material through the pharynx and into the esophagus without entry into the larynx and respiratory tract (6). This means that movement of a bolus and movement of air must be coordinated by swallow remodeling of respiratory pattern to close the airway while and bolus is moving through the pharynx. The brainstem contains respiratory and swallow neural control centers that generate the neuromuscular pattern for breathing and swallow (7, 11, 21). Swallow is an induced behavior and breathing is an automatic rhythmic behavior, hence, it is necessary for brainstem swallow neural generators to reconfigure the respiratory motor pattern to inhibit inspiration, generate a swallow breathing apnea, close the glottis and initiate the motor pattern for movement of the bolus through the pharynx. Thus, the focus of this review is the neural mechanisms for the swallow brainstem pattern generator reconfiguration of the respiratory neural network for the generation of a swallow breathing pattern.

The brainstem respiratory neural network participates in several airway defensive behaviors including: swallow, augmented breath, expiration reflex, aspiration reflex, asphyxic response, apnea, sneeze, laryngeal adduction and cough (1, 2, 4, 7, 18). All of these airway defensive behaviors require reconfiguration of respiratory pattern from normal ventilation to a unique coordinated neuromuscular pattern characteristic of the defensive reflex. With these multiple discrete airway defensive reflexes, each specific behavior brainstem neural generator is hypothesized to assume control of the respiratory neural network by a mechanism (4) referred to as behavioral control assemblies (BCA). Each of these behaviors

can be produced in an orderly and coordinated fashion (12, 13), even though the control system is bombarded with sensory information from both the pharynx and larynx. This process is consistent with decision making by the brainstem control system.

Swallow reconfiguration of respiratory pattern has been demonstrated by Jafari, et al (9) where a swallow resulted in a cessation of inspiratory activity, brief expiratory airflow followed by apnea during the activation phase of submental EMG activity, an increase in hypoglossal pressure indicating movement of the bolus through the pharynx, followed by expiratory airflow and a resumption of ventilatory breathing pattern. Hence, normal respiratory neural pattern was reconfigured to produce a swallow breathing pattern appropriate for protecting the upper airway from aspiration and simultaneously allowing the movement of the bolus through the pharynx and into the esophagus. Dick, et al (5) reported that superior laryngeal nerve (SLN) stimulation at amplitudes that elicited swallow resulted in an inhibition of inspiration characterized by a prolongation of the late phase of expiratory duration. Saito, et al (16) reported SLN stimulation induced fictive swallow and inhibited phrenic nerve inspiratory activity while simultaneously activating hypoglossal nerve activity associated with the fictive swallow. It appears that fundamental to the swallow breathing pattern is an inspiratory inhibition, swallow apnea, for a duration sufficient to allow passage of a bolus through the pharynx preventing inhalation of a portion of the bolus (aspiration) into the larynx. The swallow breathing pattern is thus the result of activation of the brainstem swallow pattern generator acting on the respiratory neural network to change the neural output to the respiratory muscles for generating swallow apnea, ie reconfiguration of the respiratory neural network.

Many of the same elements that participate in the neurogenesis of breathing also contribute to the production of cough, swallow, emesis and other reflexes that require modulation of breathing pattern (1, 2, 20). The same elements that participate in the neurogenesis of two very different behaviors was referred to as reconfiguration by Lindsey, Shannon and coworkers (1, 2, 10, 20). The concept of reconfiguration posits that a functionally connected network of neurons can produce more than one behavior by undergoing rearrangements of their discharge patterns as well as the manner in which they functionally interact to modify the motor output of the system. Reconfiguration indicates that the system has undergone a process of reorganization so that it can produce a different behavior (4). It has also been shown (Figure 1) that eliciting multiple defensive reflexes simultaneously results in discrete behaviors that can be interspersed but not coincident, again supporting the concept of discrete BCA's that reconfigure the respiratory neural network to generate a specific airway defensive behavior (12, 13). In addition, analysis of breath phase timing demonstrated that swallow elicited during repetitive coughing further modulated respiratory breath phase by increasing expiratory duration (12, 13). Saito, et al (15, 16) reported that the inhibition of inspiratory duration, prolongation of expiratory duration in breath phase timing coincident with recruitment of hypoglossal nerve activity was a function of depolarizing and hyperpolarizing currents in expiratory neurons in the respiratory neural control network. In addition they report that some neurons within this network did not respond to the swallow stimulus (15). Their results demonstrate that the recruitment of the swallow BCA generates a swallow neural drive to the respiratory control system that regulates respiratory network neurons, hence modulating breathing pattern during swallow.

To determine the neural mechanisms of swallow control of respiratory pattern, several investigators have used microelectrode recordings within the medulla in experimental animals (8, 14, 16–18). Neurons were initially classified (21) based on their activity during breathing (Figure 3). Neurons that discharge in phase with inspiration are labeled I neurons, E neurons are those the discharge in phase with expiration, neurons with activity that span the transition from expiration to inspiration are labeled E/IE and neurons that do not

discharge in phase with respiration are called non-respiratory modulated, NRM, neurons. The neurons are further classified according to their augmenting (AUG) or decrementing (DEC) activity pattern (21). It is been demonstrated with recording individual neurons that swallow will increase the activity of a subpopulation of E-DEC neurons while other E-DEC neurons are inhibited during the swallow (18). Multiple E-AUG respiratory neurons also have different swallow response characteristics, ie. inhibited during swallow motor activity but active during the inter-swallow expiratory time (18). Thus, a subpopulation of E-DEC neurons are activated during the motor phase of the swallow and active throughout expiratory duration with no swallow activity and inhibited during inspiration. Another subpopulation of E-AUG are inhibited during the swallow motor phase but are activated during the non-swallow late expiratory phase. Individually recorded inspiratory neurons were inhibited during the motor phase of swallow and a subpopulation were inhibited during the late expiratory phase while another subpopulation of I neurons are active during the late expiratory phase (18). Based on the recording of neural activity in the brain stem, Ertekina and Aydogdu (7) proposed that the swallow control of breathing pattern was an interaction between the dorsal swallow group located in the nucleus of the tractus solitarius (NTS) and the ventral swallow group located within the ventral lateral medulla. The dorsal swallow group receives activating input from supramedullary brain centers and peripheral sensory stimuli. The dorsal swallow group then interacts with the ventral swallow group to generate the swallow motor pattern. The ventral swallow group has efferent projections to the motor nerves controlling the muscles related to swallow and breathing. This general conceptualization of swallow control of breathing is consistent with a swallow BCA (4) regulating and reconfiguring the existing elements of the medullary respiratory neural network and recruiting medullary motor output to swallow specific muscles.

This hypothesized swallow BCA reconfiguration of the respiratory neural network was investigated by Bolser, Morris and colleagues (1, 2, 14, 19, 20) using simultaneous recordings of multiple brainstem neurons during breathing, swallow and cough. Recording NRM neurons (Figure 2), they found some tonic active neurons facilitated and other tonic active neurons inhibited during the motor phase of a swallow (3). They also found that these same neurons had different behavior patterns with other airway defensive reflexes such as laryngeal adduction (Figure 2). It has also been found that swallow recruited brainstem neurons were excited, inhibited, unaffected or had complex activity patterns (14). Further, there were neurons that responded to swallow only, cough only, responded in the same manner to both cough and swallow and responded in opposite manners to cough and swallow (3, 14). These observations are consistent with a swallow BCA as a recruited system of neurons. These observations are also consistent with discrete and separate brainstem BCA's sharing common neural elements while retasking those neural elements in a behavior specific manner. This research group (3) further extended their multi-electrode recording observations of respiratory and NRM neurons (Figure 3). Neurons were initially categorized during eupneic breathing. Inspiratory, expiratory, E/IE and NRM neurons were identified and recorded simultaneously (Figure 3). Liquid swallows and fictive coughs were induced. A NRM neuron was activated during the motor phase of the swallow but was quiescent during breathing and fictive cough. Some E-DEC neurons were activated during swallow while another E-DEC neuron was inhibited. These same neurons also responded in the same manner to fictive cough. E/IE-DEC neurons were activated during swallow and fictive cough. A subpopulation of I-DEC and I neurons were transiently active at the end of the swallow motor phase and during the inspiratory phase of the fictive cough. Other I-DEC and I-AUG neurons were inhibited during swallow but active during fictive cough (Figure 3). Cross correlation analysis of multiple neuron recordings in another animal was focused on a recruited NRM neuron. The NRM neuron was recruited during the motor phase of the swallow. The NRM neuron shared a common activation with an E-DEC expiratory laryngeal neuron. Another E-DEC neuron was excited during swallow by the recruited NRM and had

a subsequent reciprocal inhibition of the NRM neuron. Swallow activation of the NRM neuron excited yet another E-DEC neuron within the neural network. Connectivity analysis from this multineuronal recording experiment showed that a NRM neuron was inactive during eupneic breathing but was activated during swallow. The recruited NRM had excitatory and inhibitory connections to inspiratory and expiratory neurons with specific excitatory connections to E-Dec neurons. In addition, activation of some E-DEC neurons prolonged expiration by inspiratory inhibition. This preliminary analysis of swallow control of the respiratory neural network suggests swallow recruited NRMs may participate in reconfiguration of respiratory neural network activity pattern to prolong expiration, inhibit inspiration and generate swallow apnea.

Lindsey, Shannon and colleagues developed a model of the brain stem respiratory control network and the modulation of this network by airway defensive reflexes laryngeal and tracheobronchial cough (21). This model has been adapted here to include the swallow BCA (Figure 4). Excitatory input during swallow is proposed to originate from peripheral afferents and supramedullary neural elements. These inputs project to the dorsal swallow group for initiation of the swallow motor pattern. The dorsal swallow group drives the motoneurons of the ventral swallow group. There is connectivity between the swallow central pattern generator neurons and elements of the respiratory central pattern generator. E- AUG neurons change the temporal features of their discharge such that they are inhibited during the swallow motoneuron activation phase and are active between swallows during sustained expirations. According to the model, the duration of discharge of E- AUG early neurons and caudal expiratory bulbospinal neurons is limited by inhibition from a subpopulation of expiratory augmenting neurons (E-AUG late) that discharge in the latter portion of the expiratory phase. E- AUG late neurons have limited activity in the early expiratory phase because of inhibition by expiratory decrementing neurons (E-DEC). Swallow induced E- DEC neuron recruitment and sustained activation is present in single neuronal and multielectrode recordings. E- DEC suppression of inspiration, swallow apnea, is primarily by alteration of the duration of the late portion of the expiratory phase. The proposed role in the current model of E- DEC neurons in inhibiting inspiratory neuron activation suggests that the magnitude of expiratory activation during swallow should be related to expiratory phase duration. The model suggests that there is a direct relationship between the magnitude of expiratory motor drive and swallow apnea phase duration. Thus, activation the swallow BCA reconfigures the behavior of the respiratory neural network to generate a swallow breathing pattern that inhibit inspiration, closes the glottis and moves a bolus through the pharynx.

The model was subsequently used to computer simulate (*in silico*) respiratory neuron behavior (12) in response to activation of swallow 2nd order neurons (Figure 5). A change in the recruited swallow input to the network was eliciting by recruited NMR input, which modulated I-driver, I-AUG, E-DEC, I-DEC neural activity (Figure 5). The resultant motor nerve output was characteristic of the swallow breathing pattern including swallow apnea (Figure 5). Recruitment of the swallow BCA under these conditions elicited repetitive swallowing which was followed by an extended period of simulated breathing. This simulation predicted that the network was capable of producing repetitive swallow during inspiratory inhibition (swallow apnea). The simulation predicted *in vivo* regulation of the respiratory neural network, indicating that the predictive nature of the model is useful in guiding *in vivo* experiments particularly during changes in physiological state. Modeling the swallow BCA control of the respiratory network allows us to predict the effect of changing the gain (drive) of each element independently then testing the model *in vivo*.

In summary, swallow control of respiration is proposed to be through recruitment of swallow neural elements that retask existing respiratory neural network elements by changes

in neuronal discharge patterns. Recruitment of the swallow central pattern generator also causes suppression of existing elements resulting in removal or de-emphasis of their role in the network. Recruitment of previously silent elements may: a) add additional or different motor drive to premotor systems and b) subserve substitution where important elements are replaced by others that have different axonal connectivities. Swallow is initiated by recruitment of swallow neurons in the dorsal and ventral swallow groups. Once initiated, the swallow pattern generator produces a stereotypical motor pattern recruiting quiescent muscles and capturing control of active muscles, particularly respiratory muscles. Swallow neural control of breathing is a neural network that can reconfigure the respiratory neural output with swallow and respiration having integrated neural elements. When the bolus enters the pharynx and shares the same anatomical space for swallow and breathing, respiratory motor pattern becomes subservient to swallow within limits of respiratory drive. Swallow reconfiguration of the respiratory neural network is fundamental to airway protection and integrated with other airway protective reflexes. Thus, swallow, breathing, cough, and other airway defensive behaviors are produced by a central neural motor system that “shares” elements. The respiratory network reconfigures or “changes” to produce a variety of behaviors, most of which are important in airway defense. However, the coordination between swallow and airway defensive reflex control of breathing is poorly understood yet critical for airway protection. It is hypothesized that swallow and airway defensive behaviors are controlled by a novel recruited BCA system that is organized in a fashion that allows for precise coordination of the expression of these behaviors to maintain airway protection. Future studies are needed to determine the makeup of this control system and how it is impaired in pathological conditions.

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Figure 1.

Example of triggering swallow during repetitive cough (12, 13). Swallows occur during the cough E2 phase and result in its prolongation. Cough was induced by mechanical stimulation of the intrathoracic trachea. Swallow was initiated by transient infusion of water into the pharynx. Thin bar beneath PES trace-cough stimulus, thick bar beneath PES trace-swallow stimulus, TH-thyropharyngeus muscle EMG, GH-geniohyoid muscle EMG, ADD-adductor (thyroarytenoid) EMG, TA-transversus abdominis EMG, PS-parasternal EMG. PES units cm H₂O.

Figure 2.

Example behavioral selectivity in the caudal medial medulla (13). Swallow was initiated by transient infusion of water into the pharynx and laryngeal adduction by mechanical stimulation of the larynx. The top 3 traces are of neurons recorded simultaneously in the ventral caudal medulla. Thin bar beneath PES trace-cough stimulus, thick bar beneath PES trace-swallow stimulus, ThHy – thyrohyoideus muscle EMG, ThPy-thyropharyngeus muscle EMG, GeHy-geniohyoid muscle EMG, ADD-adductor (thyroarytenoid) EMG.

Figure 3.

Example neuronal and muscular behavioral in response to breathing, cough and swallow (3). Fictive cough was elicited by stimulation of the superior laryngeal nerve. Swallow was initiated by transient infusion of water into the pharynx. The top 16 traces are of neurons recorded simultaneously in the caudal medulla. The traces represent nerve spike histograms of extracellular recorded neuron action potentials. The neurons were labeled according to their respiratory related activity: I – inspiratory, E – expiratory, E/IE – phase spanning expiratory-to-inspiratory, NRM- non-respiratory modulated. The neurons were further classified according to: AUG – augmenting, increasing action potential frequency over the activity phase, DEC – decrementing decreasing action potential frequency over the activity phase. The bottom 4 traces moving-time averaged electromyogram activity from the following nerves: PHR - phrenic nerve, LUM – lumbar abdominal nerve, RLN – recurrent laryngeal nerve, and MYP – hypoglossal nerve.

Figure 4. Preliminary model for the neurogenesis of swallow-breathing coordination (adapted from (21)). Second order swallow behavioral control assembly (Swallow BCA) is postulated to receive swallow related afferent input (red lines). When the swallow BCA is activated, these neurons project to specific neural elements of the respiratory neural network (red lines). Results from swallow induced stimulation of the Swallow BCA suggest neurons with shared afferent input and reciprocal inhibition relay to the swallow (green lines) and respiratory motor neurons. Also represented are the Cough BCA's for laryngeal and tracheobronchial induced cough. Definitions: NTS – nucleus of the tractus solitaries, DSG – dorsal swallow group, I-DRIVER - Inspiratory neuron also active during the expiratory-inspiratory phase transition, I-Dec - Inspiratory neuron with decrementing firing rate during the phase, I-Aug - Inspiratory neuron with augmenting firing rate during the phase, I-Aug (premotor) - Inspiratory neuron with augmenting firing rate during the phase axon projects down spinal cord, E/EI - Phase spanning-starts in E ends in I, E-Dec - Expiratory neuron with decrementing firing rate most active during the early-expiratory (post-inspiratory) interval, E-Aug (early) - Rostral VRC/Böt expiratory neuron with augmenting or symmetrical discharge pattern begins activity early in phase and active throughout, E-Aug (late) - Rostral VRC/ Böt expiratory neuron with augmenting discharge pattern activity limited primarily to late part of expiratory interval (stage 2 expiration), E-Aug - Caudal expiratory neuron with

augmenting discharge pattern propriobulbar axon confined to brainstem, E-Aug (premotor) -
Expiratory neuron with augmenting discharge pattern premotor excitatory bulbospinal.

Figure 5.

In silico simulation of swallow and cough (12). Using the model in Figure 4, this figure presents the modeled reconfiguration of the output from respiratory network neurons and motor neurons. ILM – inspiratory laryngeal motor neuron, ELM – expiratory laryngeal motor neuron, IHM – inspiratory hypoglossal motor neuron, EHM – expiratory motor neuron.