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Role of the dorsal medulla in the neurogenesis of airway protection

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ABSTRACT

The dorsal medulla encompassing the nucleus of the tractus solitarius (NTS) and surrounding reticular formation (RF) has an important role in processing sensory information from the upper and lower airways for the generation and control of airway protective behaviors. These behaviors, such as cough and swallow, historically have been studied in isolation. However, recent information indicates that these and other airway protective behaviors are coordinated to minimize risk of aspiration. The dorsal medullary neural circuits that include the NTS are responsible for rhythmogenesis for repetitive swallowing, but previous models have assigned a role for this portion of the network for coughing that is restricted to monosynaptic sensory processing. We propose a more complex NTS/RF circuit that controls expression of swallowing and coughing and the coordination of these behaviors. The proposed circuit is supported by recordings of activity patterns of selected neural elements *in vivo* and simulations of a computational model of the brainstem circuit for breathing, coughing, and swallowing. This circuit includes separate rhythmic subcircuits for all three behaviors. The revised NTS/RF circuit can account for the mode of action of antitussive drugs on the cough motor pattern, as well as the unique coordination of cough and swallow by a meta-behavioral control system for airway protection.

1. Introduction

Airway protection is the prevention and/or correction of aspiration. Aspiration is prevented by the pharyngeal phase of swallow, which closes the vocal folds, changes the breathing pattern, and protects the laryngeal orifice by appropriate movement of the epiglottis. Additional behaviors, such as laryngeal adduction and apnea, also participate in the prevention of aspiration. If aspiration occurs, cough corrects this problem by the production of high velocity airflows that create shear forces to dislodge and eject material from the airway [1,2].

In contrast to the high importance of airway protective behaviors in preventing or correcting aspiration, relatively little is known about how they are regulated. Until recently, the various behaviors that contribute to protecting the airway were studied primarily in isolation. Impetus for a more unified approach has come from clinical studies that have established a strong relationship between objective metrics of cough and swallow impairment in patients at high risk of aspiration [3–5]. Further, objective metrics of cough can predict risk of aspiration with high values of sensitivity and specificity [4,6]. More recently, specific spatiotemporal coordinating processes between cough and swallow have been discovered that indicate the response to aspiration actually represents a meta-behavior [7,8]. In this context, the term meta-behavior represents multiple different behaviors that are actuated and controlled by the nervous system as a functional unit to prevent and limit the consequences of aspiration. Impairment of both cough and swallow across multiple neurological disorders in patients at risk for aspiration provides further support for the existence of a control system in which the normal execution of these behaviors is linked by common neurological mechanisms.

The nature of this control system has been probed with pharmaceutical approaches, employing intra-arterial and direct microinjection routes of administration. These studies have focused on either cough or swallow as endpoints of the airway protection control system. Progress in understanding the central mechanisms of airway protective behaviors has included identification of a functional gating mechanism for coughing that is separate from the brainstem circuit for breathing. Further, the caudal medulla has cough suppressant circuits that can be actuated by microinjection of excitatory amino acid agonists, GABA receptor agonists, or several cough suppressants drugs including codeine and nicotine [9–13].

Abbreviations: Aug, augmenting; Dec, decrementing; DSG, dorsal swallow group; E, expiratory; hyp, hypoglossal; I, inspiratory; NTS, nucleus of the tractus solitarius; RF, reticular formation; SLN, superior laryngeal nerve; VL, ventrolateral; VRC, ventral respiratory column; VSG, ventral swallow group.

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Work in the rabbit has indicated that a site of action of cough suppressants is in the nucleus of the tractus solitarius (NTS) [14–18]. Collectively, these studies support an anatomically disseminated circuit that is sensitive to the effects of cough suppressant drugs. However, they also highlight an important role for the NTS in the mechanism of action of these drugs.

2. Current understanding of the role of the NTS in mediating cough and swallow

Airway sensory feedback related to coughing is processed by second order interneurons located near to and in various subnuclei of the NTS [19,20]. The NTS cough-related circuit has been proposed to have primarily a relay function for transmission of information downstream including the ventrolateral (VL) medulla, midline raphe nuclei, and pons [21–24]. The core of the cough network is proposed to be located in the VL medulla and is hypothesized to participate in breathing and rhythm regulation for cough [21,23–26]. In the rabbit, microinjection of cough suppressants into the NTS modifies cough cycle durations [16,17]. This pattern of perturbation is typically associated with the function of a rhythm generator. These observations suggest that the role of the NTS in the neurogenesis of coughing is more extensive than "sensory pass through". Further, these studies emphasize the incomplete knowledge base that exists regarding the NTS circuits that represent potential antitussive-sensitive elements.

Like cough, the minimal neural circuitry for generation of a swallow is restricted to the brainstem, although suprapontine mechanisms can modify swallowing [27]. Swallow is also mediated by the NTS and surrounding circuits as well as by the ventrolateral (VL) medulla [27]. Jean proposed that the core of the swallow circuit is in and around the NTS and termed this area the dorsal swallow group (DSG) [27]. He also identified the "ventral swallow group" (VSG) in the VL medulla tasked primarily with motor and premotor control of the upper airway [27]. This hypothesis is based on activity patterns of neurons in NTS and medial reticular formation as well as in the VL medulla during swallow as well as results following perturbations of the DSG including microinjection of neurotransmitter agonists and antagonists [27–30]. This region, along with the surrounding medial reticular formation, has been proposed to process and shape vagal sensory information that induces swallowing [27,31]. Jean and co-workers [27,31,32] concluded that the dorsal swallow group had a sensory processing function because short latency neuronal responses to electrical stimulation of the superior laryngeal nerve were frequently observed in the NTS region relative to longer latency responses of neurons to this stimulus that were seen in the ventrolateral medulla. However, microinjection of NMDA and glutamate into the NTS induces rhythmic swallowing [28,33] and lesion of this area eliminates swallowing induced by electrical stimulation of supra-pontine structures [34], which supports a role for this medullary region in rhythmogenesis of this behavior. The roles of other brainstem regions known to contain swallow-responsive neurons and/or receive anatomical projections from the DSG/VSG, such as the pons and rostromedial reticular formation, are not fully understood [27]. The conclusions of Jean and co-workers regarding the role of the NTS and surrounding reticular formation in sensory processing and swallow rhythmogenesis highlight the critical importance of this area in airway protection.

3. Proposed coupled oscillator model of the medullary circuit controlling cough, swallow, and breathing

Our recent computational modeling efforts have been focused on NTS circuits the support the production of cough and swallowing. This computational model has been informed by a variety of different studies, including the results of multi-electrode recordings from brainstem neurons that participate in cough, swallow, and breathing [19,21,22,24,35–49]. These recordings of neuronal spike trains have been analyzed with a variety of methods intended to provide information regarding functional connectivity between neurons. Spike train cross correlation is the most common method that has been employed and is an average of the firing rate of a target neuron triggered by spikes in a reference cell. Significant differences from background firing rates allow interpretations regarding functional connectivity between the neurons. Several classes of connectivity can be inferred from features in the cross correlation histograms [50,51]. A central peak suggests inputs shared by the two neurons and/or a one-way excitatory interaction. A peak offset in time relative to the trigger event suggests excitation of the target neuron or an unobserved shared input that influences both cells with different delays. An offset trough suggests an inhibitory process, defined as any mono- or pauci-synaptic relationship that reduces target cell firing probability following trigger neuron spikes. Cross-correlation and related approaches do not allow a unique determination of the underlying neural circuit. Their goal is to define a restricted set of possible connections [52]. As such, computational models constructed based on metrics of functional connectivity between neurons represent plausible networks based on the data. For example, functional connectivity between neuronal populations in Fig. 1 is shown as "synapses" that are coded as excitatory or inhibitory and that coding is based on accumulated experimental data from cross-correlation (and other related methods) between members of the designated populations.

Simulations of the computational model were implemented through a *C* language network simulation program written for the UNIX environment. The program includes the functionality of the program SYSTM11 [53] used in previous simulations of the respiratory network [37]. The simulated networks include both discrete "integrate and fire" (IF) populations with cell parameters similar to those in SYSTEM 11 and a "hybrid" IF conditional burster" population with parameters based on the model of Breen et al. [54]. The latter population uses Hodgkin–Huxley style equations for subthreshold currents. The program allows neuron excitability to be modulated by injected current and added noise. The program also incorporates features found in NSM 2.0 [55] that aid modeling of brainstem respiratory networks, including a population type that mimics pulmonary slowly adapting stretch receptors. IF models are generally stochastic in nature, but they can be integrated with deterministic models [48]. The brainstem circuit shown in Fig. 1 is proposed to control breathing, coughing, and swallowing. This model depicts a circuit map that has been simulated as an IF (stochastic) model, but a similar network arrangement has been simulated as part of a hybrid stochastic/deterministic model that includes detailed equations that describe pulmonary and respiratory mechanics [48] during cough and breathing. The circuit does not include the pons.

Simulations with the model produce cough airflows similar to those observed in humans, and has, as noted, generated predictions on circuit mechanisms for gain control of inspiratory motor drive during cough that were subsequently supported by coordinated *in vivo* experiments [56,57]. The NTS circuit has been informed by the activity patterns of neurons recorded in the region of the NTS during cough and swallow and simulations of the proposed swallow oscillator (Fig. 2) [27,58]. This proposed circuit represents the simplest model that is consistent with the data but not been informed by specific knowledge of functional relationships with other elements of the network. A recent study using herpes simplex virus by McGovern et al. [59] mapped central pathways from the extrathoracic trachea and identified a large neuronal network in the NTS and surrounding areas. These transneuronal tracing results indicate that the size and complexity of the dorsal brainstem network for processing tracheal afferent information have been