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Production of reflex cough by brainstem respiratory networks

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Abstract

Delineation of neural mechanisms involved in reflex cough is essential for understanding its many physiological and clinical complexities, and the development of more desirable antitussive agents. Brainstem networks that generate and modulate the breathing pattern are also involved in producing the motor patterns during reflex cough. Neurones of the ventrolateral medulla respiratory pattern generator mutually interact with neural networks in the pons, medulla and cerebellum to form a larger dynamic network. This paper discusses evidence from our laboratory and others supporting the involvement of the nucleus tractus solitarii, midline raphe nuclei and lateral tegmental field in the medulla, and the pontine respiratory group and cerebellum in the production of reflex cough. Gaps in our knowledge are identified to stimulate further research on this complicated issue.

Keywords: Medullary ventral respiratory group; Pontine respiratory group; Nucleus tractus solitarii; Raphe nuclei; Lateral tegmental field; Cerebellum

1. Introduction

Cough is a modified respiratory act that can be initiated by two separate mechanisms, reflex cough and voluntary cough. Cough in conscious humans involves a complex integration of brainstem reflex mechanisms and voluntary cortical control [1]. Studies reviewed here concentrate on reflex cough by brainstem neural networks. Delineation of neural mechanisms controlling and producing reflex cough is essential for understanding its many physiological and clinical complexities. Significant progress has been made in the past 10 years [2–6].

It is now clear that the brainstem networks generating and modulating the breathing pattern are also involved in producing the motor patterns of reflex cough and other airway defensive reflexes (i.e. expiration reflex, sneeze). Neurones in the ventrolateral medulla (Bötzinger, Pre-Bötzinger and rostral Ventral Respiratory Group, Böt-VRG) that generate the respiratory pattern mutually interact with neural networks in the pons and medulla to form a larger dynamic network. These other subnetworks include the nucleus tractus solitarii, midline raphe nuclei and lateral tegmental field in the medulla, and the pontine respiratory group and cerebellum. There is a general consensus that the entire network is essential for the production of a normal breathing pattern and ventilatory responses to respiratory reflexes. In an effort to better understand the larger brainstem respiratory network and its processing of the cough reflex, we have focused on determining interactions (i.e. connectivity) among cough responsive neurones in the distributed network.

We recorded simultaneous changes in discharge patterns of many respiratory modulated and non-respiratory modulated neurones in the brainstem during fictive cough in decerebrated, neuromuscular blocked, ventilated cats. Cough-like inspiratory and expiratory motor patterns were elicited by mechanical stimulation of the intrathoracic trachea, and sometimes the larynx. Spike train analysis methods (i.e. cross correlation, spike triggered averaging) were used to search for concurrent functional interactions among respiratory neurones in the networks (for details of methods see 2–4)

As an example of the involvement of the distributed brainstem respiratory network in the cough reflex, Fig. 1 illustrates alterations in the patterns of simultaneously

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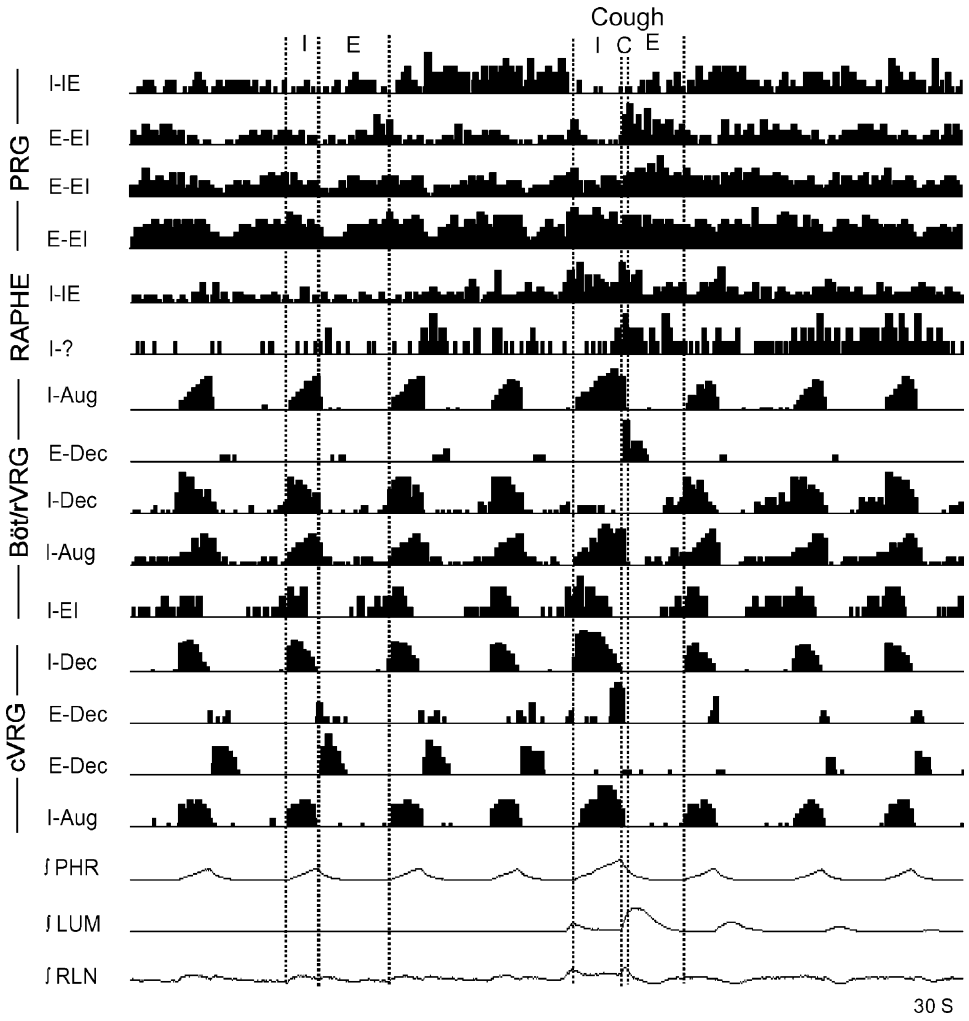

Fig. 1. Firing rate histograms of simultaneous responses of respiratory modulated neurones in the Pontine Respiratory Group, midline raphe nuclei, and rostral (Böt-VRG) and caudal Ventral Respiratory Groups during a cough episode. Respiratory discharge patterns were determined by cycle-triggered histograms (e.g. Fig. 2B). Abbreviations: E, neurone with peak activity during the expiratory phase; I, neurone with peak activity during the inspiratory phase; EI, activity spans the expiratory–inspiratory transition; IE, activity spans the inspiratory–expiratory transition; Aug, augmenting—peak firing rates in the last half of the phase; Dec, decrementing—peak firing rates in the first half of the phase; Question mark (?), could not determine discharge pattern. ∫PHR, LUM and RLN, integrated (time-moving average, 200 ms time constant) of phrenic, lumbar and recurrent laryngeal nerve motor activities; Cough I, C and E; neural inspiratory, compressive and expulsive phases of cough. The fictive cough cycle is indicated by the large increase in phrenic and subsequent lumbar nerve activities.

recorded respiratory modulated neurons in the rostral (Böt-VRG) and caudal Ventral Respiratory Groups, Pontine Respiratory Group, and midline raphe nuclei during a cough episode.

In addition to these areas of the brainstem, this review will include other studies of ours on the nucleus tractus solitarii [7,8] and cerebellum [9], and the work of others on the lateral tegmental field [10,11].

2. Nucleus tractus solitarii (NTS)

Cough receptors project to relay neurones in the NTS [12]. Based on studies of airway rapidly adapting irritant receptors [13,14], it is presumed that NTS cough relay neurones have a widespread effect on the brainstem respiratory network through polysynaptic pathways. Target neurones are unknown.

We conducted experiments to characterize NTS neurones involved in the cough reflex elicited from the trachea [7,8]. Neurone activity was recorded from the commissural nucleus region caudal to the obex, which contains most of the tracheobronchial irritant receptor 2nd order relay neurones [13,15] and presumably cough relay neurones. Some cells were excited or inhibited and their change in activity appeared to be dependent on the intensity and duration of tracheal stimulation. This group included cells with weak respiratory modulation, no respiratory modulation and silent ones recruited during stimulation. Another group of weakly respiratory modulated cells increased firing rates coincident with the respiratory phases of cough, as well as increased tonic activity, suggesting they also receive feedback from the cough pattern generator (Böt-VRG).

We had hypothesized that airway cough receptors and their NTS relay neurones would be silent during normal breathing. The varied responses of tonically active cells suggested that the processing of cough afferent information in the NTS and its transmission to other areas also includes a network of active neurones.

The response of neurones in the commissural nucleus region to mechanical stimulation of the larynx [8] was also examined. The objective was to assess possible convergence of cough afferent stimuli from the trachea and larynx. Most laryngeal receptor afferent fibres project to regions of the NTS rostral to the obex and medial to the dorsal respiratory group [16]. We observed neurones that were excited or inhibited by only one of the stimuli, while others were excited and/or inhibited by both stimuli. These results suggested that a subpopulation of interneurones in cough reflex pathways receive afferent information from both laryngeal and tracheobronchial cough receptors.

We also obtained simultaneous recordings of cough responsive NTS and Böt-VRG neurones to test for functional connections using cross-correlation analysis of spike-trains (unpublished). There were no short-latency offset features in the correlograms suggestive of direct excitatory or inhibitory influences in either direction. These results are consistent with, but do not prove, the absence of direct connections, suggesting the existence of interneurones in the pathways. Bolser and colleagues [6,17] have proposed the existence of a functional 'gate' (i.e. interneurones) through which cough afferent information passes.

3. Bötzinger, pre-bötzinger, ventral respiratory group (Böt-VRG)

Results from our studies enabled us to propose a comprehensive network model for the participation of Böt-VRG neurones in the generation of cough motor patterns in respiratory pump (diaphragm, intercostal and abdominal) and laryngeal muscles [2–4,6]. A schematic representation of an updated model is shown in Fig. 4. Excitatory and inhibitory connections onto respiratory bulbospinal premotor neurones, that drive spinal motoneurones, and upper airway (i.e. laryngeal) motoneurones arise from subpopulations in the 'core' network (enclosed by dotted lines). The sequence and patterns of neurone activity during cough and their synaptic interactions is presented in a recent review [6].

4. Caudal medullary raphe nuclei

Elements of the midline caudal medullary raphe (magnus, obscurus) nuclei modulate breathing. This respiratory related network includes primarily tonic firing cells, with some exhibiting weak respiratory modulated firing rates (Fig. 2B), that mutually interact with the Böt-VRG [18,19]. The neurones are proposed to transmit and transform sensory information that influences breathing, modulate respiratory drive, and have a stabilizing influence on the respiratory pattern produced by the Böt-VRG.

Midline neurones are essential for expression of the cough reflex. Kainic acid destruction of cells in the raphe nuclei and adjoining reticular formation altered the control respiratory pattern and eliminated cough patterns in spinal respiratory motoneurones [20]. These results are consistent with the view that an intact brainstem respiratory network is essential for the production of a normal breathing pattern and ventilatory responses to respiratory reflexes.

As a next step in understanding the mechanisms by which raphe neurones participate in the cough reflex, we examined discharge patterns during fictive cough [21]. Responses of inspiratory, expiratory and non-respiratory modulated neurones are illustrated in Fig. 2A. There were enhanced and attenuated inspiratory, expiratory and tonic changes in neurone firing rates. The predominant response was an increase in non-respiratory related (tonic) activity lasting longer than the cough episodes. The probable source of the control and enhanced respiratory modulation of the neurones is the Böt-VRG [18]. The complex, prolonged changes in activity were due most likely to the effects of recurrent interactions with other brainstem sites as well as within the raphe network [18]. Whether there are inputs from NTS cough relay neurones is unknown. We have evidence for actions of vagal afferents (i.e. pulmonary stretch receptors) on respiratory modulated raphe neurons [22], but whether this interaction affects the cough reflex is yet to be studied.

In other studies, we described respiratory-related neuronal assemblies in the midline of the medulla that have reciprocal interactions with the ventrolateral medullary respiratory network [18,19,23]. In the cough reflex studies, we observed a few cell-cell correlations suggestive of reciprocal connectivity between these two regions (unpublished). There are insufficient cross-correlation data to expand the Böt-VRG network model (Fig. 4) to include reciprocal connections with raphe neurones that would explain the influence of raphe neurones on eupnoic breathing and the cough reflex. Collectively, our studies are consistent with the emerging picture of raphe neurones as integrators of afferent input and modulators through efferent actions on brainstem motor and autonomic control systems [24].

5. Pontine respiratory group (PRG)

The network of neurones referred to as the Pontine Respiratory Group, in the rostral dorsal lateral pons (medial parabrachial and Kölliker-Fuse nuclei and the lateral pons/mesencephalic junction) is essential for a normal breathing pattern [25]. It influences respiratory phase durations by interaction with the rhythm and pattern

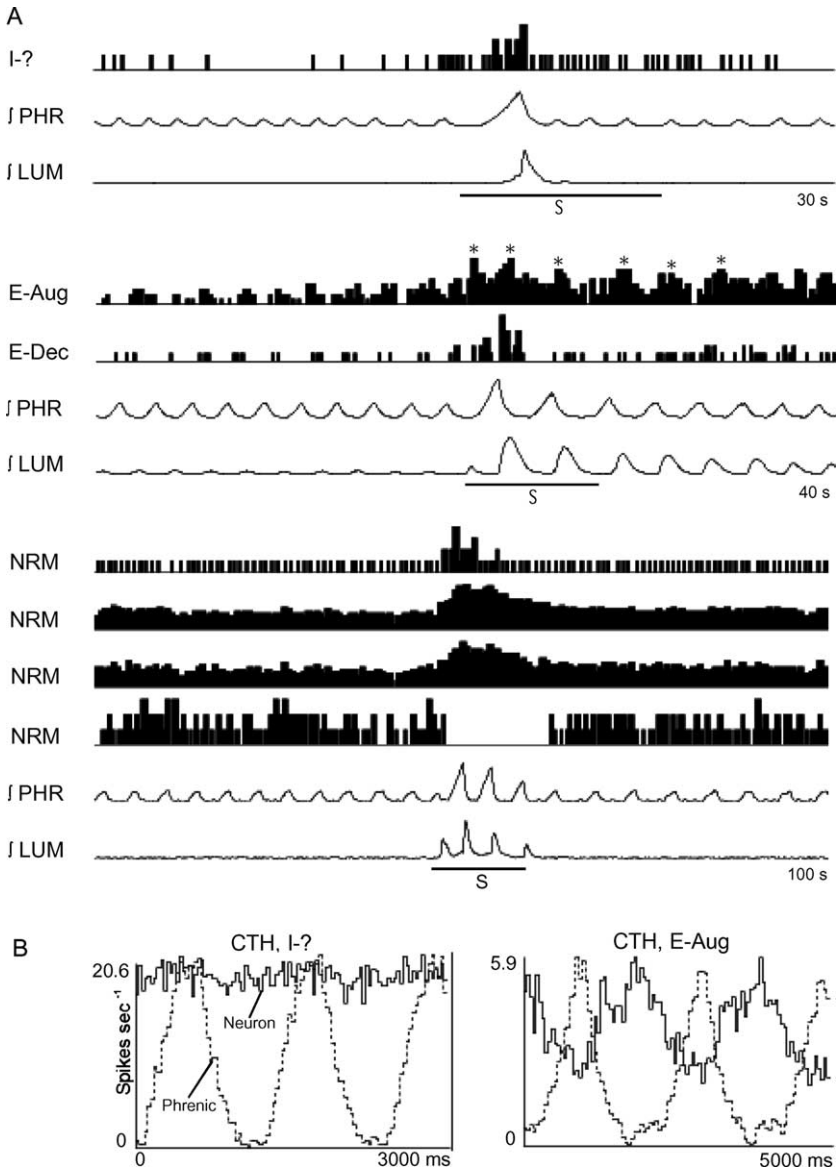

Fig. 2. (A) Response of midline raphe neurones during fictive cough. NRM, non-respiratory modulated. S, duration of stimulus. Asterisks in second panel indicate increased firing rate associated with the expiratory phase of the cough cycles. (B) Cycle-triggered histograms (CTH) of neurones in the panels one and two. Firing rates (in spikes/sec^{-1}) refer to the largest bin in the corresponding plot.

generating network in the medulla (Böt-VRG). This pontine network is also required for appropriate responses of the brainstem respiratory network to stimulation of respiratory reflexes [26].

Evidence supporting involvement of the PRG in the cough reflex was presented recently by Poliacek et al. [27]; kainic acid inactivation of neurones in the region of the dorsal lateral pons, that includes the Pontine Respiratory Group, eliminated cough responses. These results imply that the Böt-VRG requires interaction with the Pontine Respiratory Group in order to generate the cough motor pattern.

In an effort to understand further the role of the PRG in the expression of the cough reflex, we examined neurone discharge patterns during fictive cough in cats [28]. Most PRG neurones were tonically active with inspiratory, expiratory and phase-spanning discharge patterns during control cycles (Fig. 3B). There were complex changes in the patterns during fictive cough, but generally the firing rates of respiratory modulated neurones increased during the same phase in which they were more active during the control period (Fig. 3A). Neurones with no respiratory modulation or that were silent during control cycles also changed activity during cough; the changes were associated with the inspiratory and expiratory phases of the cough cycle.

Mechanisms responsible for PRG neurone firing patterns during eupnoea or coughing are unknown. Current models suggest that eupnoic patterns include inputs from Böt-VRG neurones [29,30], interactions among PRG neurones [31,32] and inputs from pulmonary stretch receptor relay neurones in the NTS [33]. In addition to these elements, discharge

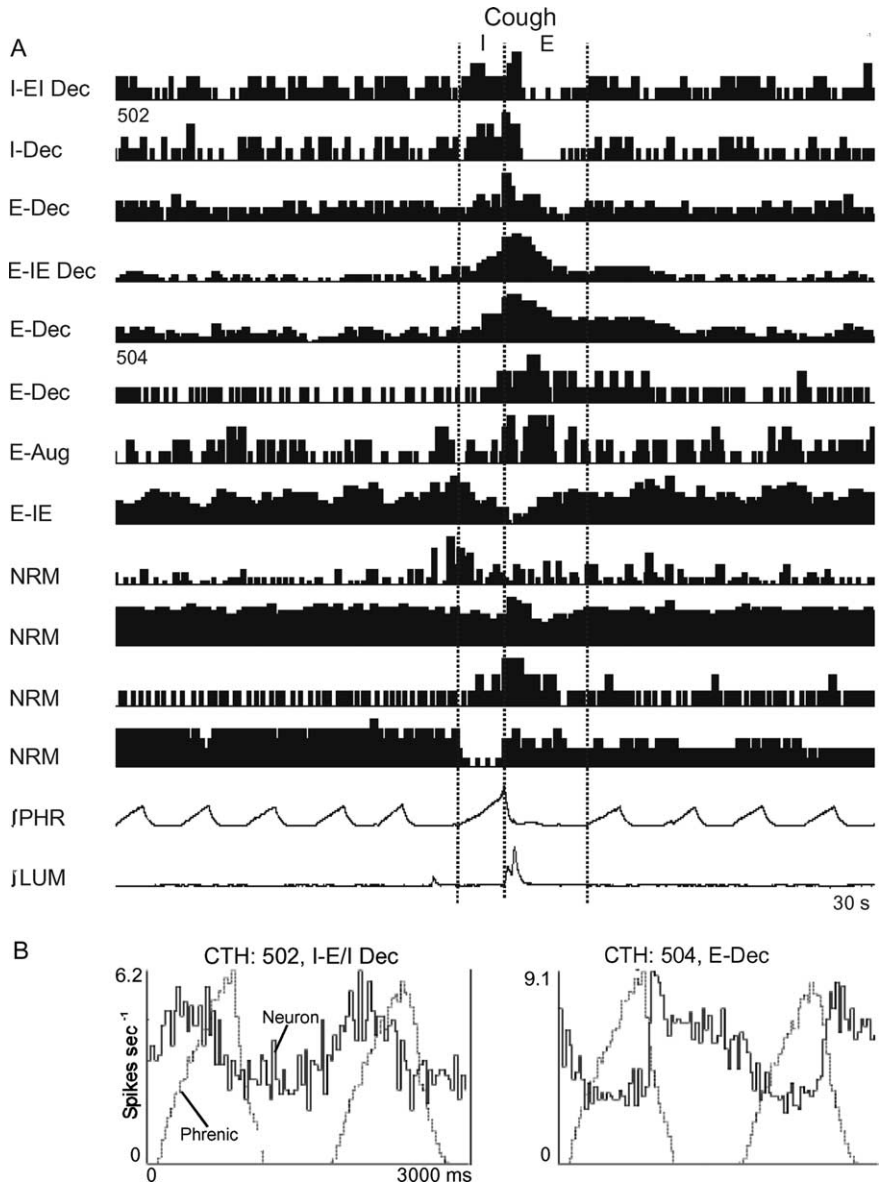

Fig. 3. (A) Pontine neurone responses during fictive cough. (B) Examples of cycle—triggered histograms.

patterns during cough are likely to be influenced by inputs from NTS cough receptor relay neurones and the cerebellum (and of course conscious inputs in awake subjects).

Results from our neurone study are consistent with the PRG receiving inputs from Böt-VRG neurones (Fig. 4). During cough, the response patterns of inspiratory and expiratory modulated cells were similar to those observed in subgroups of Böt-VRG neurones with comparable control discharge profiles [2,3]. The question still unanswered is, to what extent the changes in PRG activity reciprocally affect Böt-VRG neurones and thus cough pattern formation?

We also observed that vagal input (i.e. pulmonary stretch receptors) influenced the discharge patterns of neurones in the PRG [34]. It attenuates the magnitude of respiratory modulation and alters the discharge patterns during control cycles. Pulmonary stretch receptors are known to have a 'permissive' effect on reflex cough [35]. The effect of pulmonary stretch receptors on PRG activity during cough, or the importance of this interaction in the permissive mechanism, needs further study.

6. Cerebellum

Early in the development of our experimental preparation, we discovered that it was more difficult to elicit fictive cough following removal of the cerebellum to expose the dorsal surface of the brainstem for insertion of recording microelectrodes. A collaborative study with Xu et al. [9] confirmed this anecdotal observation. The primary alteration in cough responsiveness following cerebellectomy, or lesioning of the interposed nucleus, was a reduction in

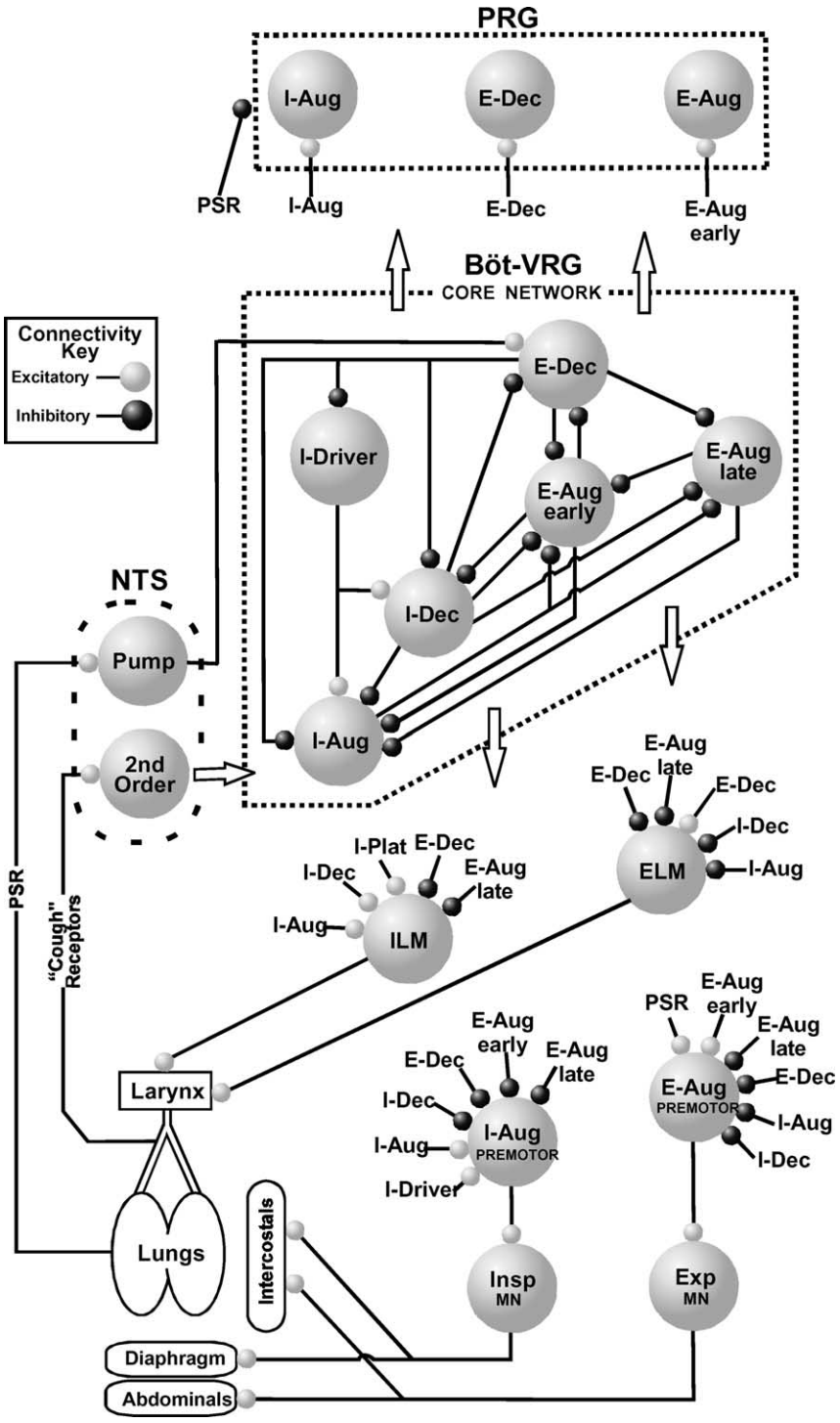

Fig. 4. Scheme of Böt-rVRG respiratory neuronal core network (enclosed by dotted line box) with input from pulmonary stretch receptor (PSR) Pump cells. Nucleus tractus solitarius (NTS) cough receptor 2nd-order neurones influence the network through unknown pathways. Neurone connections onto respiratory bulbospinal premotor neurons (I-Aug and E-Aug) and laryngeal motoneurones (ILM and ELM) arise from the core network. Pontine Respiratory Group (PRG) cells also receive input from the core through unknown pathways. E-Aug Early and E-Aug Late, neurones that begin discharging prior to and during the latter part of the expiratory phase, respectively. I-Driver, inspiratory neurone also active before the expiratory–inspiratory phase transition and with a relatively constant discharge rate throughout the inspiratory phase. I-Dec and E-Dec, inspiratory and expiratory modulated neurones with decrementing patterns. MN, motoneurones. For detailed description of the core of the model, see Shannon and co-workers [2,3]. An update of the sequence and patterns of neurone activity during cough and their synaptic interactions is presented in a recent review [6].

the number of coughs (cough frequency) generated by a maximum stimulus. There was also a reduction in peak discharge rate in abdominal expiratory motor nerves.

The deep cerebellar nuclei (i.e. fastigial, interposed and infracerebellar/lateral) modulate breathing, particularly during respiratory stresses [36]. These nuclei contain cells with respiratory modulated firing rates due to afferent information from pulmonary stretch receptors and presumably Böt-VRG neurones [36]. The mechanisms by which the cerebellar and brainstem respiratory neural networks interact to modulate cough patterns need further study. One hypothesis for multiple cough cycles following a brief stimulus is that the first cycle is produced by the Böt/VRG which then sends an efference copy to the cerebellum; feedback from the cerebellum stimulates an oscillation in cough patterns by the Böt-VRG which is ultimately damped-out. Cerebellar output to the Böt-VRG could also be modulated by cough receptor and pulmonary stretch receptor [36] relay neurone inputs from the NTS. A role of the cerebellum in cough is consistent with its known functions of sensory-motor integration and motor coordination, learning and timing.

7. Lateral tegmental field

The lateral tegmental field (LTF) in the medulla integrates and modulates a variety of reflexes, including those involved in respiratory control. It contains weakly respiratory-modulated cells [37]. Non-respiratory-modulated neurones with projections to the spinal cord have been shown to increase activity during the laryngeal expiration reflex [38]. C-fos expression during fictive cough and its elimination with codeine suggested that LTF neurones participated in the cough reflex [39].

Kainic acid destruction of cells in the nucleus reticularis ventralis and the adjacent parts of the rostral medullary LTF altered the eupnoic breathing pattern and eliminated cough and expiration reflex motor responses [40]. The critical injection site for suppression of the reflexes was located between the dorsal and ventral respiratory groups. These results imply that neurones in the LTF network have an important role in maintaining the responsiveness of the Böt-VRG network to afferent inputs, in a manner similar to the PRG and raphe networks. Of course, the LTF could also be a critical relay network for afferent information to the eupnoic/cough generation network (Böt-VRG). The mechanisms and pathways by which the medial LTF influences breathing and cough reflexes are yet to be studied.

8. Conclusions

The brainstem networks generating and modulating the breathing pattern are also involved in producing the motor patterns of reflex cough, and other airway defensive reflexes (i.e. expiration reflex, sneeze). Very little is known about the interaction within and among these networks (nucleus tractus solitarii, Böt-VRG, midline raphe nuclei, lateral tegmental field, pontine respiratory group and cerebellum). It would not be surprising if other areas of the brainstem found to alter the eupnoic respiratory pattern also influence the responsiveness of cough and other respiratory reflexes.

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References

[1] Lee PCL, Cotterill-Jones C, Eccles R. Voluntary control of cough. Pulm Pharmacol Therap 2002;15:317–20.
[2] Shannon R, Morris KF, Lindsey BG. Ventrolateral medullary respiratory network and a model of cough motor pattern generation. J Appl Physiol 1998;84:2020–35.
[3] Shannon R, Baekey DM, Morris KF, Li Z, Lindsey BG. Functional connectivity among ventrolateral medullary respiratory neurons and responses during fictive cough in the cat. J Physiol 2000;525:207–24.
[4] Baekey DM, Morris KF, Gestreau C, Lindsey BG, Shannon R. Medullary respiratory neurones and control of laryngeal motoneurones during fictive eupnoea and cough in the cat. J Physiol 2001;534:565–81.
[5] Pantaleo T, Bongianni F, Donatella D. Central nervous mechanisms of cough. Pulm Pharmacol 2002;15:227–33.
[6] Bolser DC, Davenport PW, Golder FJ, Baekey DM, Morris KF, Lindsey BG, et al. Neurogenesis of cough. In: Boushey H, Chung KF, Widdicombe JG, editors. Cough: causes, mechanisms and therapy. Oxford: Blackwell Science; 2003. p. 173–80.
[7] Shannon R, Morris KF, Lindsey BG. Nucleus tractus solitarius neuronal responses during fictive cough. Fed Am Soc Eur Biochem J 1995;9:A667.
[8] Bolser DC, Baekey DM, Morris KF, Nuding SC, Lindsey BG, Shannon R. Responses of putative nucleus tractus solitarius (NTS) interneurons in cough reflex pathways during laryngeal and tracheobronchial cough. Fed Am Soc Eur Biochem J 2000;14:A644.
[9] Xu F, Frazier DT, Zhang Z, Baekey DM, Shannon R. Influence of the cerebellum on the cough motor pattern. J Appl Physiol 1997;83:391–7.
[10] Jakus J, Stransky A, Poliacek I, Barani H, Boselova L. Kainic acid lesions to the lateral tegmental field of medulla: effects on cough, expiration and aspiration reflexes in anesthetized cats. Physiol Res 2000;49:387–98.
[11] Gestreau C, Bianchi AL, Grelot L. Differential brainstem fos-like immunoreactivity after laryngeal-induced coughing and its reduction by codeine. J Neurosci 1997;17:9340–52.
[12] Mazzone SB, Geraghty DP. Respiratory actions of tachykinins in the nucleus of the solitary tract: characterization of receptors using selective agonists and antagonists. Br J Pharmacol 2000;129:1121–31.

[13] Kubin L, Davies RO. Central pathways of pulmonary and airway vagal afferents. In: Dempsey JA, Pack AI, editors. Regulation of breathing. Lung biology in health and disease, vol. 79. New York: Marcel Dekker; 1995. p. 219–84.
[14] Ezure K, Otake K, Lipski J, Wong She RB. Efferent projections of pulmonary rapidly adapting receptor relay neurons in the cat. Brain Res 1991;564:268–78.
[15] Lipski J, Ezure K, Wong She RB. Identification of neurons receiving input from pulmonary rapidly adapting receptors in the cat. J Physiol 1991;443:55–77.
[16] Lucier GE, Egizil R, Destrovsky JO. Projections of the internal branch of the superior laryngeal nerve in the cat. Brain Res Bull 1986;16: 713–21.
[17] Bolser DC, Davenport PW. Functional organization of the central cough generation mechanism. Pulm Pharmacol Therap 2002;15: 221–5.
[18] Lindsey BG, Segers LS, Morris KF, Hernandez YM, Saporta S, Shannon R. Distributed actions and dynamic associations in respiratory-related neuronal assemblies of the ventrolateral medulla and brainstem midline: evidence from spike train analysis. J Neurophysiol 1994;72:1830–51.
[19] Lindsey BG, Morris KF, Segers LS, Shannon R. Respiratory neuronal assemblies. Respir Physiol 2000;122:183–96.
[20] Jakus J, Stransky A, Poliacek I, Barani H, Boselova L. Effects of medullary midline lesions on cough and other airway reflexes in anaesthetized cats. Physiol Res 1998;47:203–13.
[21] Baekey DM, Morris KF, Nuding SC, Segers LS, Lindsey BG, Shannon R. Medullary raphe neuron activity is altered during fictive cough in the decerebrate cat. J Appl Physiol 2003;94:93–100.
[22] Morris KF, Dick TE, Baekey DM, Nuding SC, Segers LS, Shannon R, et al. Changes in respiratory-modulated activity of caudal raphe neurons after acute vagotomy. Soc Neurosci Abst 2002 [program No. 570.5].
[23] Morris KF, Shannon R, Lindsey BG. Changes in cat medullary neurone firing rates and synchrony following induction of respiratory long-term facilitation. J Physiol 2001;532(2):483–97.
[24] Lovick TA. The medullary raphe nuclei: a system for integration and gain control in autonomic and somatomotor responsiveness? Exp Physiol 1997;82:31–41.
[25] John St WM. Neurogenesis of patterns of automatic ventilatory activity. Prog Neurobiol 1998;56(1):97–117.
[26] Bianchi AL, Denavit-Saubie M, Champagnat J. Central control of breathing in mammals: neuronal circuitry, membrane properties, and neurotransmitters. Physiol Rev 1995;75:1–45.
[27] Poliacek I, Jakus J, Stransky A, Barani H, Halasova E, Tomori Z. Cough, expiration and aspiration reflexes following kainic acid lesions to the pontine respiratory group in anaesthetized cats. Physiol Res 2004;53:155–63.
[28] Shannon R, Baekey DM, Morris KF, Nuding SC, Segers LS, Lindsey BG. Pontine respiratory group neuron discharge is altered during fictive cough in the decerebrate cat. Respir Physiol Neurobiol 2004;142:43–54.
[29] Feldman JL, Cohen MI, Wolotsky P. Powerful inhibition of pontine respiratory neurons by pulmonary afferent activity. Brain Res 1976; 104:341–6.
[30] Shannon R, Lindsey BG. Intercostal and abdominal muscle afferent influence on pneumotaxic center respiratory neurons. Respir Physiol 1983;52:85–98.
[31] Dick TE, Bellingham MC, Richter DW. Pontine respiratory neurons in anesthetized cats. Brain Res 1994;636:259–69.
[32] Morris KF, Dick TE, Baekey DM, Nuding SC, Segers LS, Shannon R, et al. Brainstem cardiorespiratory network interactions. Fed Am Soc Eur Biochem J 2004;18(3):844 [Abstracts].
[33] Shaw C-F, Cohen MI, Barnhardt R. Inspiratory-modulated neurons of the rostrolateral pons: effects of pulmonary afferent input. Brain Res 1989;485:179–84.
[34] Dick TE, Morris KF, Baekey DM, Nuding SC, Segers LS, Lindsey BG, et al. Dorsolateral pontine respiratory modulated activity before and after vagotomy in decerebrate cats. Soc Neurosci Abst 2002 [program No. 171.1].
[35] Hanacek J. Reflex inputs to cough. Eur Respir Rev 2002;12(85): 259–63.
[36] Xu F, Frazier DT. Role of the cerebellar deep nuclei in respiratory modulation. Cerebellum 2002;1:35–40.
[37] Fung ML, Tomori Z, John St WM. Medullary neuronal activities in gasping induced by pharyngeal stimulation and hypoxia. Respir Physiol 1995;100:195–202.
[38] D'iachenko I, Preobrazhenkii N. Responses of bulbo-spinal neurons during the expiration reflex in cats. Neirofiziologiia 1991;23:88–98 [in Russian].
[39] Gestreau C, Bianchi AL, Grelot L. Differential brainstem fos-like iummunoreactivity after laryngeal-induced coughing and its reduction by codeine. J Neurosci 1997;17:9340–52.
[40] Jakus J, Stransky A, Poliacek I, Barani H, Boselova L. Kainic acid lesions to the lateral tegmental field of medulla: effects on cough, expiration and aspiration reflexes in anesthetized cats. Physiol Res 2000;49:387–98.