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A POSSIBLE ROLE OF THE PONS IN NORMAL RESPIRATORY RHYTHM GENERATION: INSIGHTS FROM COMPUTATIONAL MODELING

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Introduction

The normal respiratory pattern ("eupnea") in mammals is generated in the lower brainstem and may involve several medullary and pontine regions (e.g., [10]). Although some medullary regions, in particular, the pre-Bötzinger Complex, can generate a respiratory-related rhythm *in vitro* [8, 9, 12] the eupneic breathing pattern has never been reproduced in reduced medullary preparations without the pons. Such preparations also cannot reproduce apneusis, an abnormal breathing pattern characterized by sustained or significantly prolonged inspiration. These observations support the concept that respiration-related pontine regions are necessary parts of the brainstem respiratory network responsible for the generation of eupnea [2, 15, 19, 20]. Furthermore, the specific ponto-medullary interactions involved in the generation, shaping and control of the respiratory pattern have not been well characterized. Here we present and analyze a computational model of the ponto-medullary respiratory network and compare its performance with the existing experimental data.

Model description

The model (Fig. 1) contains interacting populations of respiratory neurons that have been characterized in the rostroventolateral medulla and pons *in vivo*. The medullary component of the model includes three major regions: rostral ventral respiratory group (rVRG), pre-Bötzinger Complex (pre-BötC), and Bötzinger Complex (BötC). The pontine component is conditionally subdivided into a rostral (rPons) and caudal (cPons) parts. The neural populations of the rPons in the model are considered to perform the functions of the respiratory areas located in the dorsolateral and ventrolateral pons. The cPons is assumed to contain a part of the pontine reticular formation that partly provides excitatory tonic drive to the medulla. The following neural populations have been included in the model: ramp- and (aug-E) (in BötC); inspiratory modulated (I), expiratory modulated (E) and two distinct inspiratory- expiratory modulated (IE_1 and $IE_{2)}$ (in rPons,), and tonic (in cPons). All neurons are modeled in the Hodgkin-Huxley style and incorporate biophysical properties characterized in respiratory neurons *in vitro.* Specifically, the fast sodium and persistent sodium currents (the latter is included only in pre-I neurons) are described using recent experimental data [16] the high- and low-threshold calcium currents are described using data of Elsen and Ramirez [3] intracellular calcium dynamics was based on data of Frermann et al. [4]; other cellular parameters are accepted from the previous models [14, 17]. Each population consists of 50 neurons. Neuronal parameters are randomized over each population with some variance.

Some connectivities among the medullary neural populations were assigned based on published direct and indirect data. Other connections included in the model have not been studied and are open for testing; these were assigned to support the inspiratory off-switch (IOS) and expiratory off-switch (EOS) mechanisms incorporated. The network interactions within rVRG (i.e., between the ramp-I, early-I, and late-I populations) and between rVRG and BötC populations define the basic circuitry for IOS mechanism. The late-I population plays the key role in the initiation of inspiratory off-switching [1, 6, 11, 13] providing inhibition of the early-I population. The latter disinhibits the post-I population that completes switching to expiration. Interactions among rVRG populations, post-I population and pre-I population of pre-BötC define the basic circuitry for the EOS mechanism with the pre-I population explicitly performing the inspiratory on-switching (and hence the EOS) function [5]. During expiration, the pre-I population is inhibited by the post-I population. When the pre-I

population fires, after a release from inhibition, it provides the initial activation to the early-I and ramp-I populations, which complete switching to inspiration.
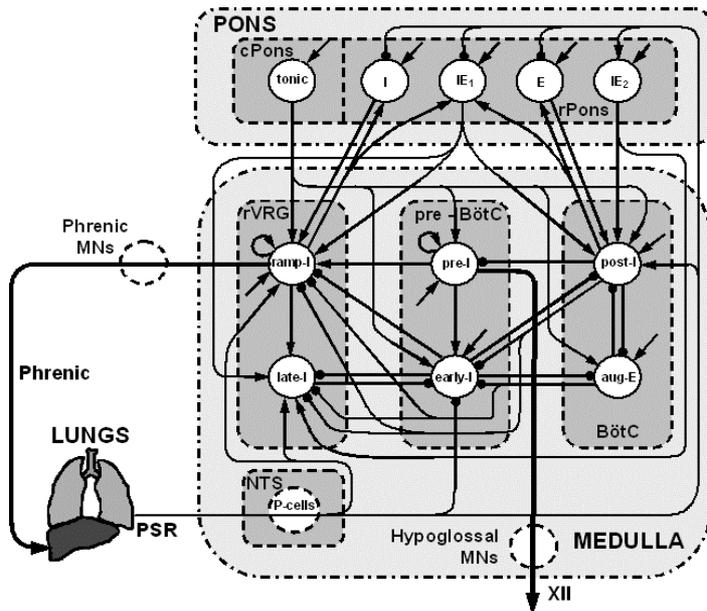

Fig. 1. Schematic of the model of the ponto-medullary respiratory network. The white circles represent different neuron populations (see the text) (the populations of phrenic and hypoglossal motoneurons and NTS pump (P) cells are not present in the current model). Arrows and small black circles show excitatory and inhibitory synaptic connections respectively.

Reciprocal excitatory connections were assigned between the medullary ramp-I and the pontine I and IE_1 populations, and between the medullary post-I and the pontine IE_1 and E populations providing I, IE or E modulation of activity of the corresponding populations. We, therefore, suggest the existence of topically organized bidirectional mapping between the BötC-VRG areas in the medulla and the corresponding respiration-related areas in the rostral pons [6, 12]. We also suggest that a sub-population of excitatory post-I neurons is present in BötC-VRG and projects post-inspiratory excitation to the pons (see also [18]). At the same time, some pontine populations, e.g., IE_2 in our model, may receive excitation from pulmonary stretch receptor afferents. In addition, we assume that reticular neurons from the caudal pons (the tonic population) may provide an additional excitatory tonic drive to the medullary respiratory neurons.

Integrated activities of medullary ramp-I and pre-I populations are considered phrenic and hypoglossal outputs respectively. Simplified models of the lungs and slowly adapting pulmonary stretch receptors (PSR) were included in the model to provide pulmonary feedback to the respiratory network. The pulmonary feedback controls the activity of the key neural populations involved in the IOS and EOS mechanisms (activates the late-I, post-I and ramp-I populations and inhibits the early-I population) and suppresses activity of the pontine neural populations that receive excitation from the medullary populations (I, IE_1, E). Importantly, the IOS and EOS mechanisms operate under control of both pontine input and pulmonary feedback that are both excitatory to the late-I, ramp-I and post-I populations [6, 11].

Model performance. Comparison with experimental data

The model generates a stable "eupneic" respiratory rhythm and exhibits realistic firing patterns and membrane potential trajectories of individual respiratory neurons (see Fig. 2A). Specifically, the firing bursts of individual ramp-I neurons as well as the bursts of phrenic discharges exhibit "augmenting" patterns.

Starting from Lumsden's classic work [10], many studies have demonstrated that removal of the rostral pons or chemical blockade of some respiration-related areas within this region converts eupnea to apneusis especially in vagotomized animals [1, 7, 19, 20]. A complete removal of the pons produces a gasping-like pattern [10, 19], which therefore may be generated by some mechanisms inherent to the medulla. Similarly, the removal of rPons in our model converts the eupneic pattern to apneusis (Fig. 2A1, A2), and the complete removal of the pons (additional removal of cPons) replaces apneusis with a gasping-like pattern (Fig. 2A3). Figure 2B1-B3 demonstrates similar changes in the phrenic motor pattern control conditions with pons intact (Fig. 2B1), after removal of the rostral pons (Fig. 2B2) and after the complete removal of the pons (Fig. 2B3) [20]. Figure 2A1,A3 compares the eupneic pattern generated in the model with the pons intact (A1) and the gasping-like pattern produced after complete removal of the pons (A3). In our model, the loss of the rPons reduces excitatory input to the post-I neurons and hence reduces the phasic inhibitory removal of the cPons reduces excitatory tonic drive to the medulla, specifically to the pre-I population (see Fig. 1). Both the above release the pacemaker properties of the pre-I population of in pre-BötC [17]. The intrinsic oscillations of this population may now drive the entire medullary network and produce phrenic discharges with a gasping-like pattern (Fig. 2A3) [15, 17, 20] that is similar to that recorded *in vitro*. Besides this characteristic change in phrenic pattern (from "incrementing" to "decrementing"), two other important differences between gasping and eupnea may be noticed in our

simulations. First, gasping is characterized by a significant reduction in the post-inspiratory activity (see Fig. 2A3 vs. 2A1). Second, the transition from eupnea to gasping is accompanied by a significant shortening in the delay between the onset of firing of pre-I and ramp-I neurons and between the hypoglossal and phrenic discharges (see Fig. 2A3 vs. 2A1) as was reported recently [20].
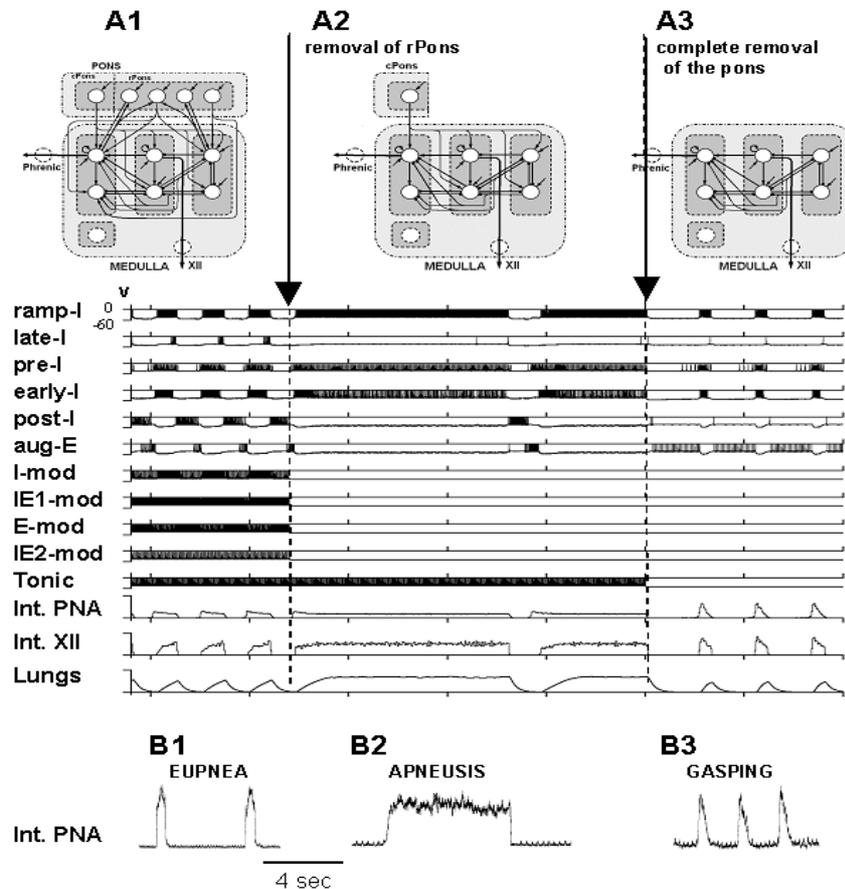

Fig. 2. Simulation of pontine lesions. **A1.** The eupneic respiratory pattern (the pons is intact). **A2.** Removal of rPons converts the eupneic pattern to apneusis. **A3.** The following removal of the cPons releases an intrinsic pacemaker-driven rhythm generated in the pre-I population of the pre-BötC and converts apneusis to a gasping-like "decrementing" discharges. **B1-B3.** Alterations in pattern of phrenic activity following brainstem transections between the pons and medulla in preparation of juvenile rat (adapted from [20] with permission). Eupnea (**B1**) was recorded in a preparation having an intact pons and medulla. Apneusis (**B2**) was observed after a transection through the dorsal half of brainstem at the ponto-medullary junction. Gasping (**B3**) followed completion of the transection.

Conclusion

The model presented here supports the concept that, under normal conditions *in vivo*, the eupneic respiratory rhythm is generated by a ponto-medullary network. Hence, although the pre-BötC is a necessary part of this network (and various perturbations applied to this area may indeed disturb the respiratory rhythm generation), the intrinsic oscillations in this region are suppressed during eupnea by ponto-medullary interactions. Specifically, our model suggests that pontine inputs activate medullary post-I neurons that, in turn, provide phasic inhibition to the pre-I population in the pre-BötC. In addition, tonic drive from the caudal pons holds the excitability of this population out of the voltage range necessary for pacemaking behavior. However, we conclude that endogenous oscillations in the pre-BötC may be released under some conditions, e.g., *in vitro*, because of the lack of the pons, or during hypoxia *in vivo* [15, 17, 20].

Acknowledgements

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SLANG: A SYMBOLIC LANGUAGE FOR DISTRIBUTED REPRESENTATION

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The development of intelligent systems and cognitive modeling requires complex hierarchical models that reflect the variety of real world situations, events, phenomena and concepts. The choice of information representation is very important for the models [1]. Usually symbolic or local representations are used, for example predicate ones. Each model component is represented there as a separate memory object and inter-object connections are implemented as pointers. Handling such models is computationally expensive because composite models do not contain immediate information about their components. In particular, model comparison require exhaustive component-wise comparison at various hierarchical levels.

In stark contrast to traditional computing where "every bit counts", in binary distributed representations [1, 2] information is distributed over large number of elements, which are modeled by high-dimensional binary vectors (*codevectors*). The meaningful entity not a single element but the total pattern over all elements. Superficially, the patterns appear random. Codevectors of hierarchical models are built from codevectors of simple models using bitwise operations ∧, ∨, etc. This ensures their equal dimensionality N, preserves information about component model and allows finding out similarity of hierarchical models just as overlap of 1s in their codevectors.