

State-dependent control of the respiratory pattern and coupled oscillators

Ilya A. Rybak¹, Ana P. L. Abdala², Yaroslav I. Molkov¹, Julian FR Paton², and Jeffrey C Smith³

¹Dept. of Neurobiology & Anatomy, Drexel University College of Medicine, Philadelphia, PA 19129, USA

²Dept. of Physiology & Pharmacology, University of Bristol, Bristol BS8 1TD, UK

³National Institute of Neurological Disorders and Stroke (NINDS), NIH, Bethesda, MD 20892, USA

Abstract

The respiratory rhythm and motor pattern are generated by a spatially organized brain stem respiratory network with a rhythmic core comprising interacting neural populations within the pre-Bötzinger (pre-BötC) and Bötzinger (BötC) complexes controlled by drives and inputs from other brain stem compartments. Our previous large-scale computational model [3, 4] reproduced the behavior of this network under multiple natural and experimental conditions, but did not consider neural oscillations that were proposed to emerge within the retrotrapezoid nucleus/parabrachial respiratory group (RTN/pFRG) and drive pre-inspiratory (or late-expiratory, late-E) oscillations in the abdominal motor output [2]. These late-E oscillations usually emerge with increasing metabolic demands (e.g., during hypercapnia or hypoxia) and couple with the respiratory oscillations generated by the BötC-pre-BötC core of the respiratory central pattern generator [1, 2].

In our experiments, performed in the arterially perfused *in situ* rat preparation, the respiratory motor activity was recorded simultaneously from abdominal, phrenic, hypoglossal and central vagus nerves. Under normal conditions (eupnea), the abdominal motor outflow showed only a low-amplitude post-inspiratory (post-I) activity. An expression of the abdominal late-E bursts, preceding and coupled to phrenic discharges, occurred during hypercapnia (7–10% CO₂) and could be abolished by pharmacological inactivation of the RTN/pFRG region and by administration of riluzole, a persistent sodium current (*I_{NaP}*) blocker, hence confirming that the late-E oscillations originate in RTN/pFRG and involve intrinsic, *I_{NaP}*-dependent mechanisms.

Using these data we extended our computational model by incorporating in the RTN/pFRG compartment an additional late-E population (with neurons containing *I_{NaP}*) serving as a source of abdominal late-E activity. The proposed interactions between the BötC's and pre-BötC's populations and the late-E population of RTN/pFRG allowed the model to reproduce several experimentally observed behaviors, including quantal acceleration of abdominal late-E oscillations with progressive hypercapnia and quantal slowing of phrenic activity with progressive suppression of pre-BötC excitability (simulating the suppressing effects of opioids), as well as to predict a release of late-E oscillations by disinhibition of RTN/pFRG under normal conditions. The latter prediction has been confirmed in our experimental studies.

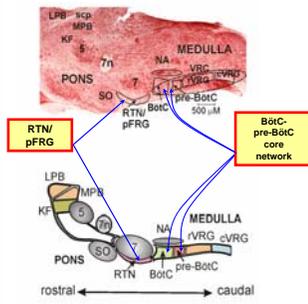
Our experimental and modeling studies suggest that under normal metabolic conditions the RTN/pFRG oscillator is inhibited by both the post-I population of BötC during inspiration and early-motoneuron (early-I) population of pre-BötC during inspiration. Therefore the late-E oscillations can be released by either a hypercapnia-evoked activation of chemosensitive RTN/pFRG neurons overcoming this inhibition or a hypoxia-dependent suppression of RTN/pFRG inhibition by BötC-pre-BötC circuits.

Our model proposes mechanistic explanations for the emergence of RTN/pFRG oscillations and their interaction with the brain stem respiratory network. The emerging view is that the brain stem respiratory network has rhythmic capabilities at multiple hierarchical levels, which allows flexible, state-dependent expression of different rhythmic mechanisms under different physiological and metabolic conditions and enables a wide repertoire of respiratory behaviors.

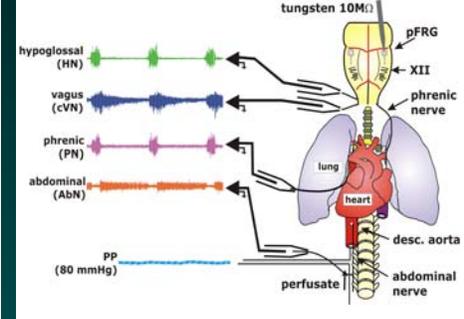
References

1. Abdala AP, Rybak IA, Smith JC, Paton JFR. Abdominal expiratory activity in the rat brain stem-spinal cord *in situ*: patterns, origins and implications for respiratory rhythm generation. *J Physiol* 2009; 587: 3529–3559.
2. Janczewski WA, Feldman JL. Distinct rhythm generators for inspiration and expiration in the juvenile rat. *J Physiol* 2006; 570: 407–420.
3. Rybak IA, Abdala AP, Marlin SN, Paton JFR, Smith JC. Spatial organization and state-dependent mechanisms for respiratory rhythm and pattern generation. *Prog Brain Res* 2007; 165: 201–220.
4. Smith JC, Abdala AP, Koizumi H, Rybak IA, Paton JFR. Spatial and functional architecture of the mammalian brain stem respiratory network: a hierarchy of three oscillatory mechanisms. *J Neurophysiol* 2007; 98: 3370–3387.

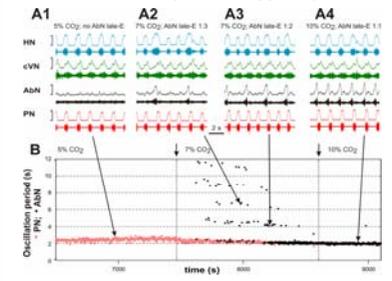
Location of BötC/pre-BötC and RTN/pFRG oscillators



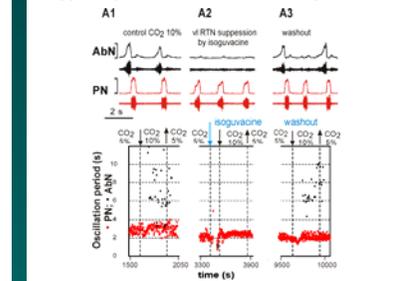
Respiratory motor outputs



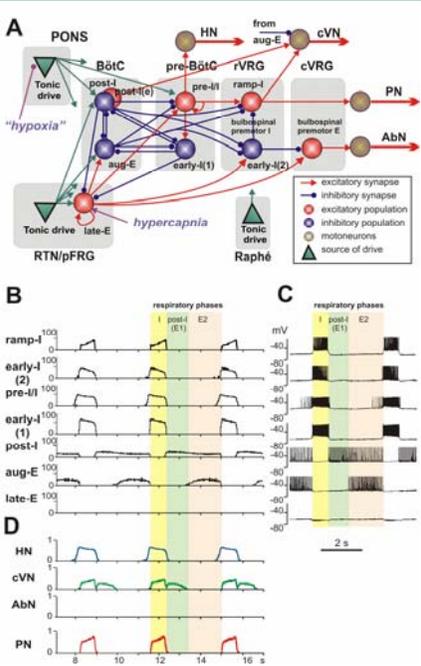
Quantal acceleration of AbN late-E activity with the development of hypercapnia



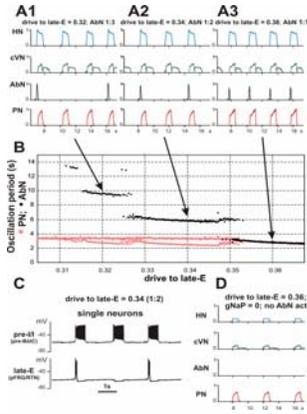
The effect of RTN/pFRG suppression on hypercapnia-evoked late-E activity in AbN



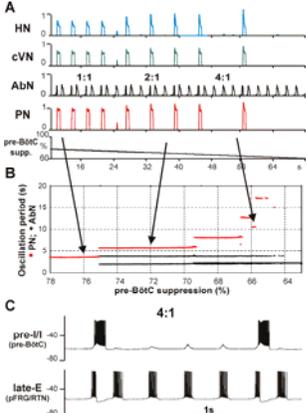
Large-scale computational model



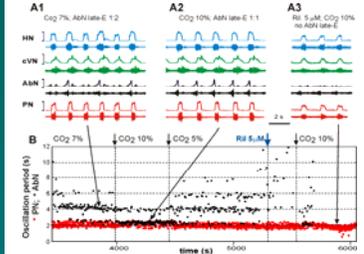
Quantal acceleration of late-E activity



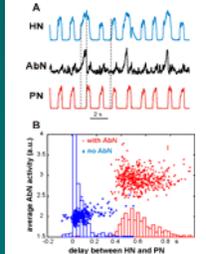
Quantal slowing of PN activity



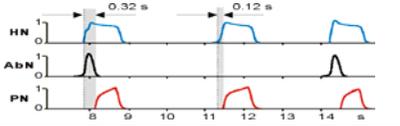
Effects of riluzole on the hypercapnia-induced AbN late-E activity



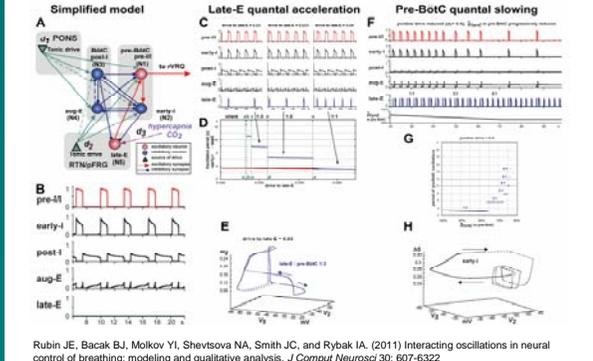
Late-E effect on the delay between HN and PN



Late-E effect on the delay between HN and PN

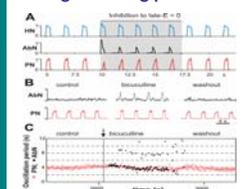


Simplified model



Rubin JE, Bacak BJ, Molkov YI, Shevtsova NA, Smith JC, and Rybak IA. (2011) Interacting oscillations in neural control of breathing: modeling and qualitative analysis. *J Comput Neurosci* 30: 607-6322

Testing modeling predictions



Proposed interactions between BötC/pre-BötC and pFRG/RTN

