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Coupled Oscillations in Neural Control of Breathing

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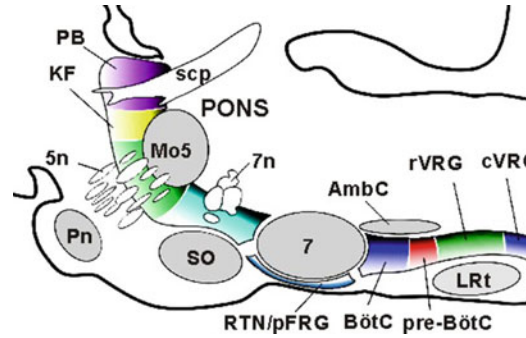
Synonyms

Dual-generator concept

Definition

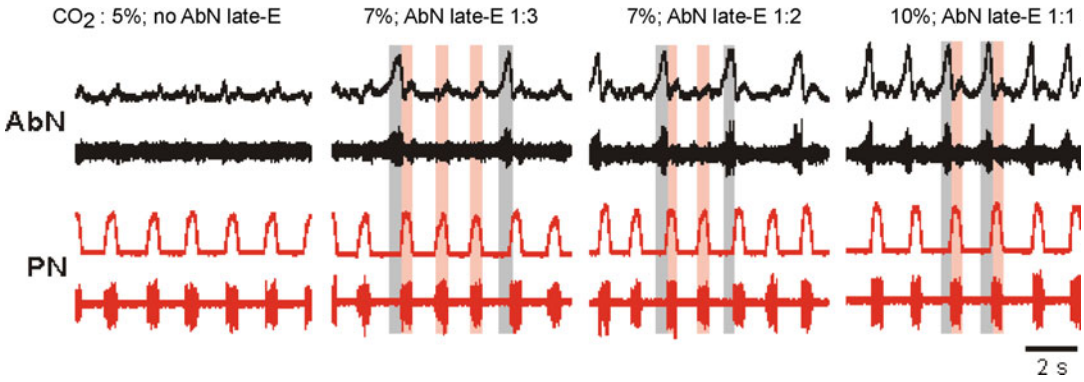
The respiratory rhythm in mammals is generated by a respiratory central pattern generator (CPG) in the brainstem and encompasses both pons and medulla (see Fig. 1; Alheid and McCrimmon 2008; Smith et al. 2013). The pre-Bötzinger complex (pre-BötC), located in the ventrolateral region of the medulla, is the putative kernel of rhythmic inspiratory activity. The pre-BötC interacts with the expiratory neurons of Bötzinger complex (BötC) to generate primary respiratory oscillations. These oscillations are defined by both the intrinsic biophysical properties of neurons involved and the network interactions within and between the pre-BötC and BötC. Through the premotor neurons of the rostral ventral respiratory group (rVRG), these oscillations produce rhythmic drive to phrenic motoneurons that through the phrenic nerve (PN) control movements of the diaphragm and lung inflation.



Coupled Oscillations in Neural Control of Breathing, Fig. 1 Parasagittal view of brainstem at the level of nucleus ambiguus. *Abbreviations*: *5n* trigeminal nerve, *7* facial nucleus, *7n* facial nerve, *AmbC* compact part of nucleus ambiguus, *BötC* bötzinger complex, *cVRG* caudal division of ventral respiratory group, *KF* kölliker-fuse nucleus, *Mo5* motor nucleus of the trigeminal nerve, *PB* parabrachial nucleus, *pFRG* parafacial respiratory group, *Pn* basilar pontine nuclei, *pre-BötC* pre-bötzinger complex, *RTN* retrotrapezoid nucleus, *rVRG* rostral division of ventral respiratory group, *scp* superior cerebellar peduncle, *SO* superior olive, *sol* solitary tract, *sp5* spinal trigeminal tract, *VRC* ventral respiratory column of the medulla, *VRG* ventral respiratory group (Adapted from Alheid and McCrimmon (2008) with permission)

A distinct site of neural oscillations involved with the respiratory function, located more rostral to the pre-BötC, was identified *in vitro*, in the isolated brainstem-spinal cord preparation. The source of these oscillations, which was termed parafacial respiratory group (pFRG), was found to reside within the retrotrapezoid nucleus (RTN) or partially overlaps with it (Onimaru and Homma 2003; Janczewski and Feldman 2006). The pFRG oscillations emerge with increased metabolic demands (e.g., hypercapnia) and via abdominal nerve (AbN) drive abdominal muscles enabling forced lung deflation (active expiration). This rhythmic activity is coupled to the pre-BötC oscillations so that generated bursts represent late-expiratory (late-E) or sometimes biphasic (containing pre-inspiratory, pre-I, and post-inspiratory, post-I, components) discharges (Janczewski and Feldman 2006; Abdala et al. 2009).

Several competing concepts concerning the appearance of RTN/pFRG oscillations and their physiological function have been suggested (Janczewski et al. 2002; Onimaru and Homma 2003; Abdala et al. 2009; Molkov et al. 2010).



Coupled Oscillations in Neural Control of Breathing, Fig. 2 Quantal acceleration of late-E discharges in the in situ brainstem-spinal cord preparation. The phrenic nerve (*PN*, *red*) and abdominal nerve (*AbN*, *black*) activities are shown by pairs of traces: raw recording (*lower trace*) and integrated activity (*upper trace*). PN bursts define inspiratory phases of respiratory cycles (some highlighted by *vertical pink bars*), and interburst intervals correspond to expiratory phases. Late-E discharges in AbN occur at the end of expiration, just prior to inspiration (highlighted by *gray bars*) (Adapted from Molkov et al. (2010) with permission)

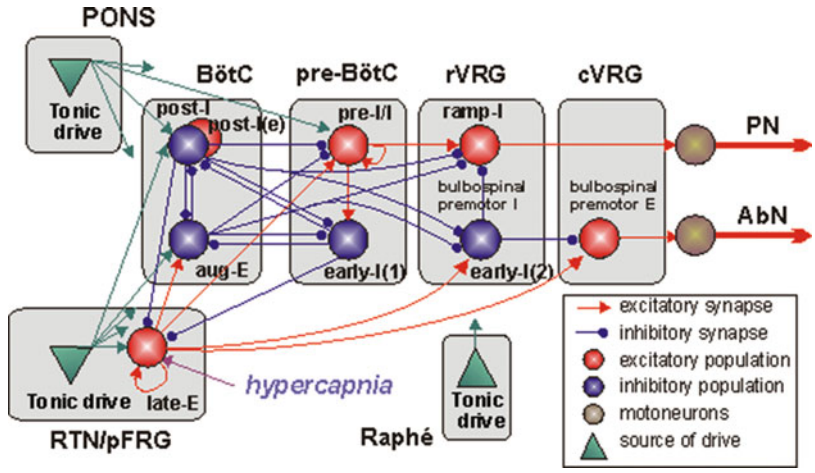
However, there are still heated debates on the exact physiological role of RTN/pFRG oscillations, the specific conditions for their emergence, and the nature and mechanisms of the interactions between the BötC/pre-BötC and RTN/pFRG oscillators.

Detailed Description

From mathematical viewpoint, the most striking experimental observations that evidence the existence of two distinct oscillators in neural control of breathing are the so-called *quantal slowing* of phrenic rhythm (Janczewski and Feldman 2006; Mellen et al. 2003) and *quantal acceleration* of abdominal discharges (Abdala et al. 2009; Molkov et al. 2010).

The *quantal slowing* of the pre-BötC and/or PN oscillations has been demonstrated with administration of opioid agonists in the *in vitro* isolated brainstem-spinal cord preparation and *in vivo* (Mellen et al. 2003; Janczewski and Feldman 2006). This phenomenon consists of a stepwise reduction in the frequency of pre-BötC (and/or PN) oscillations resulting from deletion (missing) of a single or a series of inspiratory bursts in the output activity recorded. Although the exact pharmacological effect of opioids is unknown, the general assumption has been that opioids reduce the excitability of pre-BötC neurons either directly or indirectly (via the suppression of excitatory synaptic transmission within the pre-BötC).

Similarly, *quantal acceleration* of late-E abdominal activity was observed with development of hypercapnia (elevation of CO_2) in the in situ arterially perfused rat brainstem-spinal cord preparation (Fig. 2, see Abdala et al. 2009; Molkov et al. 2010) and *in vivo* (Iizuka and Fregosi 2007). Experimental studies in the perfused in situ preparation have shown that under baseline normocapnic metabolic conditions (5 % CO_2), the abdominal nerve motor output (AbN) typically exhibits a low-amplitude expiratory (post-I) activity. Switching to hypercapnic (7–10 % CO_2) conditions evoked large amplitude late-E (also called pre-I) bursts in the AbN. These late-E discharges emerge in AbN at 7 % CO_2 followed by a progressive increase in their frequency as the CO_2 concentration in the perfusate is incremented to 10 %. Importantly, although the frequency of late-E bursts increases with CO_2, these bursts remained coupled (phase-locked) to the inspiratory bursts in the PN (Fig. 2). With the development of hypercapnia, the ratio of late-E burst frequency to the PN burst frequency showed a stepwise (quantal) increase from 1:5 and 1:4 (not shown) to 1:3, 1:2, and, finally, 1:1 (at 10 % CO_2). On returning CO_2 to



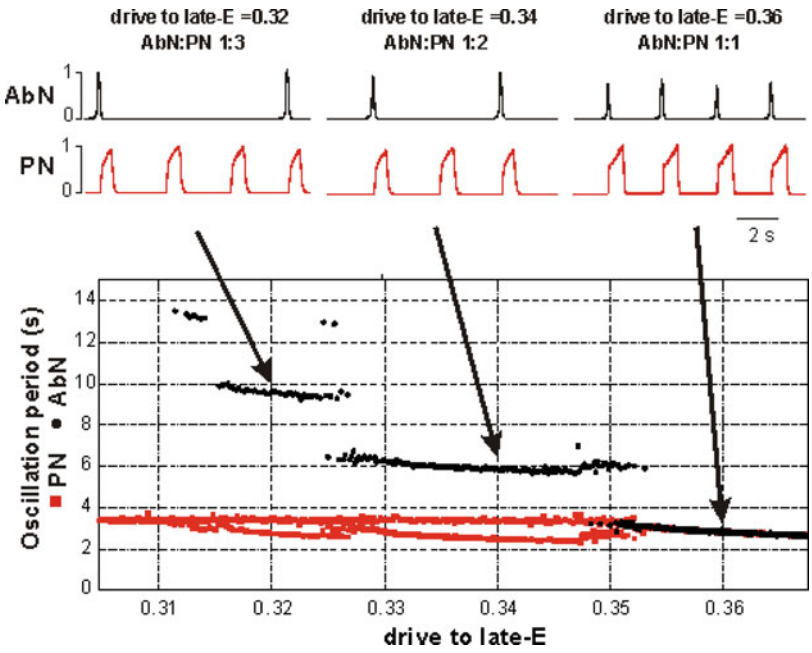
Coupled Oscillations in Neural Control of Breathing, Fig. 3 The schematic of the model. Each population (shown as a *sphere*) consists of 50 single-compartment neurons described in the Hodgkin-Huxley style. The populations are denoted according to their firing pattern: *post-I* post-inspiratory, *aug-E* augmenting expiratory, *pre-I/I* pre-inspiratory/inspiratory, *early-I* early inspiratory, *ramp-I* ramping inspiratory, *late-E* late expiratory. BötC/pre-BötC oscillator (Smith et al. 2007) controls RTN/pFRG oscillator (the intrinsically rhythmic late-E population) by inhibitory inputs from post-I and early-I(1) neurons. Excitatory late-E neurons send their axons to bulbospinal premotor expiratory (E) neurons in cVRG, representing the source of AbN activity. The model includes three sources of tonic excitatory drive: pons, RTN, and raphé (shown as *green triangles*) which project to multiple neural populations in the model. The late-E population receives an additional external drive simulating the effect of hypercapnia. All model equations and parameters can be found in Molkov et al. (2010) (Adapted from Molkov et al. (2010) with permission)

the control levels, the ratio showed a stepwise reversal.

Several computational models of interacting neural oscillators related to generation of respiratory activity with various levels of complexity have been proposed. The most detailed description of possible interactions between the BötC/pre-BötC and RTN/pFRG circuits (Fig. 3; Molkov et al. 2010) was developed as an extension of the respiratory CPG model proposed earlier by Smith et al. (2007) (see ▶ Computational Models of Mammalian Respiratory CPG). According to that description, the BötC/pre-BötC oscillator controls the emergence of late-E oscillations in RTN/pFRG and their frequency and phase by inhibiting RTN/pFRG oscillator during both expiration (via post-I inhibition) and inspiration (via early-I inhibition). This inhibition prevents late-E activity in RTN/pFRG and AbN to occur under normal metabolic conditions.

The excitability of the late-E population in RTN/pFRG in the model is highly sensitive to hypercapnia which causes their depolarization (see Fig. 3). At some level of CO_2, this excitation overcomes the inhibition of late-E population in RTN/pFRG by BötC/pre-BötC circuits and initiates late-E rhythmic activity which translates to AbN. The late-E bursts initially emerge at a very low frequency, but as CO_2 level progresses (Fig. 4), the frequency of late-E discharges quantally increases, until it reaches 1:1 ratio with the BötC/pre-BötC oscillations that define PN output. In contrast, strong hypoxia or anoxia can evoke the RTN/pFRG oscillations through a reduction of inhibition, specifically the post-I inhibition, and produce an effect similar to hypercapnia by shifting the balance between inhibition and excitation at the level of RTN/pFRG late-E neurons.

Rubin et al. (2011) performed thorough qualitative analysis of the reduced model and explained the regimes of *quantal acceleration* and *quantal slowing* in terms of synchronization of the BötC/pre-BötC and RTN/pFRG oscillators. The dynamics of each oscillator can be represented by a stable limit cycle in some

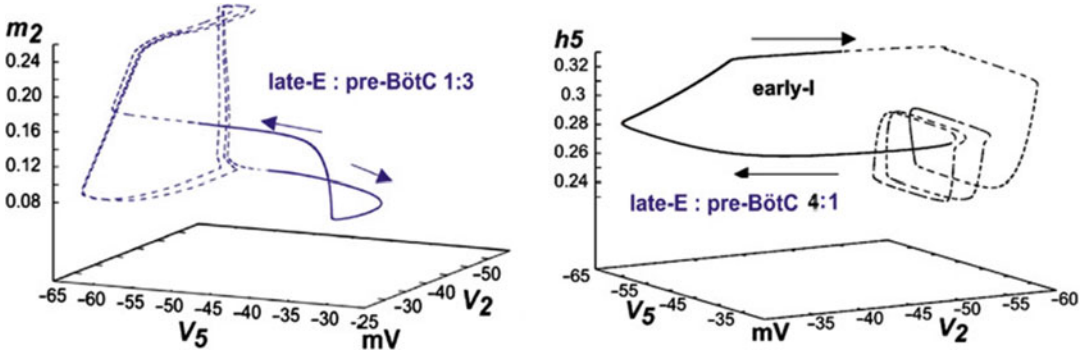


Coupled Oscillations in Neural Control of Breathing, Fig. 4 Quantal acceleration of AbN activity in the model. The late-E bursts in the AbN are always phase-locked with PN bursts, and the ratio between AbN and PN frequencies quantally increased through 1:3 (at drive to late-E = 0.32) to 1:2 (0.34) and to 1:1 (0.36) as "hypercapnic" drive to the late-E population of RTN/pFRG gradually increases mimicking progressive hypercapnia. The *lower panel* shows the dependence of oscillation periods in AbN (*black circles*) and PN (*red squares*) on the hypercapnic drive (*horizontal axis*). The period of AbN late-E discharges sequentially jumps from 4 PN periods to 3, then to 2, and finally to 1 (Adapted from Molkov et al. (2010) with permission)

phase space. The phase space of a system of two coupled oscillators is a Cartesian product of the phase spaces of each oscillator. The corresponding limit set is a 2D invariant torus, and the behavior of this system is represented by a trajectory on this torus. If the ratio of oscillation frequencies of the two oscillators is rational (i.e., equal to N/M, for some integers N and M), then this trajectory is closed, indicating N:M synchronization between oscillators, where N and M represent numbers of rotations around two orthogonal circles that together span the torus.

With changing conditions, the system of coupled oscillators can proceed through regimes characterized by different relations between oscillation frequencies. A progressive increase of RTN/pFRG excitability as defined by the CO_2 level results in an emergence and subsequent increase in the frequency of its oscillations. Due to coupling between RTN/pFRG and BötC/pre-BötC oscillators, the system proceeds through a series of phase-locked resonances with 1:N ratios between the RTN/pFRG and BötC/pre-BötC frequencies, with N decreasing from an initial higher value to 1 (N = 3 on Fig. 5). The specifics of this coupling define a phase (late-E) of RTN/pFRG oscillations in all synchronized states.

In contrast, progressive suppression of pre-BötC excitability (e.g., by opioid agonists) results in a decrease in frequency of BötC/pre-BötC rhythm generator and ultimately in cessation of its oscillations. In this regime, the pre-BötC neurons depend on recruitment by the late-E neuron to activate. Because of this coupling, the pre-BötC frequency is quantally reduced through a series of resonances with M:1 ratios between the RTN/pFRG and BötC/pre-BötC frequencies with M increasing from 1 to higher values (see M = 4 on Fig. 5).



Coupled Oscillations in Neural Control of Breathing, Fig. 5 The phase trajectories in the reduced model illustrating two synchronized late-E: pre-BötC states during hypercapnia (1:3 regime, *left panel*) and after suppression of pre-BötC (4:1 regime, *right panel*). The reduced model by Rubin et al. (2011) describes neural populations as two-dimensional relaxation oscillators with one fast and one slow variable. Fast variables V_2 and V_5 represent membrane potentials of early-I neuron in pre-BötC and late-E neuron in RTN/pFRG, respectively; m_2 and h_5 are slow variables of these oscillators. Subthreshold activities of late-E neuron (*left*) and early-I neuron (*right*) are shown by *dashed lines*. Suprathreshold parts of trajectories (*solid lines*) correspond to bursts of the late-E (*left*) and pre-BotC (*right*) neurons. Cyclical subthreshold movement on the *left panel* indicates two periods of early-I activity during which the late-E neuron fails to burst. Similar movement on the *right* shows four late-E oscillations during which pre-BotC neurons fail to activate (Adapted from Rubin et al. (2011) with permission)

Cross-References

► Computational Models of Mammalian Respiratory CPG

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Coupling of Local Field Potentials

► Local Field Potential, Synchrony of