Mechanisms Underlying Inspiratory Burst Generation in preBötzinger Complex Neurons of Neonatal Mice

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Abstract

Understanding how molecular and cellular events integrate into a physiological behavior is a major question in neuroscience. Breathing can be easily studied using rhythmically active *in vitro* models that provide experimental access to perform cellular- and synapse-level experiments. While it is widely accepted that breathing depends on a specific region of the brainstem dubbed the preBötzinger complex (preBötC), the mechanisms responsible for rhythm generation remain unclear. In Chapter 1, we examine the *pacemaker hypothesis*, which posits that pacemaker properties and/or the persistent sodium current (I_{NaP}) are obligatory for rhythm generation. We found that neither pacemaker properties nor I_{NaP} are essential for respiratory rhythm generation in preBötC neurons. Next, we began testing the validity of the *group pacemaker hypothesis*, which posits that the respiratory rhythm is an emergent network property that depends on recurrent excitation coupled to intrinsic membrane properties in all preBötC neurons. During the inspiration *in vitro*, all preBötC neurons exhibit 300-500 ms bursts of electrical activity characterized by action potentials superimposed on a 10-30 mV envelope of depolarization, dubbed the *inspiratory drive potential*. Chapters 2 and 3 examine how synaptic and intrinsic membrane properties integrate to form inspiratory drive potentials. In Chapter 2, we found that the calcium-activated non-specific cationic current (I_{CAN}) is responsible for ~70% of the inspiratory drive potential. I_{CAN} activation depends on Ca^{2+} influx from inositol 1,4,5-trisphosphate (IP_3Rs)-mediated intracellular Ca^{2+} release coupled to group I metabotropic glutamate receptors (mGluRs), voltage-gated Ca^{2+} channels (VGCCs) and possibly to a smaller extent NMDA receptors. Chapter 3 examines how AMPARs trigger inspiratory burst potential generation. We found that AMPAR-mediated depolarizations open VGCCs, which activate I_{CAN} directly. Moreover, Ca^{2+} influx from VGCC was required to trigger IP_3R-mediated intracellular Ca^{2+} release. In Chapter 4, we interpret respiratory frequency modulation within the context of the group pacemaker hypothesis. We show that blocking low-frequency AMPAR-mediated excitatory postsynaptic potentials (EPSPs) causes rhythm cessation, which suggests that low-frequency EPSPs are important for kindling the initial phase of recurrent excitation. Through a meta-analysis of previously published work, we argue that frequency modulation depends on the temporal summation of EPSPs and is largely independent of changes in interburst spiking. In conclusion, our findings suggest that respiratory rhythm generation and frequency modulation depends on the coupling of synaptic and intrinsic membrane properties, which is most consistent with the group pacemaker hypothesis.