The Origins of Inspiratory and Sign Breathing Rhythms: Ion Channels, Bursting Mechanisms, and Synaptic Topologies Studied in Vitro and in Silico.

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Abstract

Breathing is the rhythmic motor behavior that maintains homeostasis by driving gas exchange between our blood and the atmosphere. This behavior is essential for life in all terrestrial mammals. Breathing involves two distinct but coupled rhythms: the inspiratory rhythm, the normal breathing rhythm that occurs on the order of seconds, and the sigh rhythm, which produces large amplitude breaths that occur on the order of minutes and maintain pulmonary function. Both behaviors originate in a specialized neuronal region of the ventral medulla called the preBötzinger complex (preBötC). However, the mechanism by which they are generated remains the subject of debate. We used a suite of experiments that utilized transgenic mouse models to falsify a long-standing theory that intrinsically rhythmic neurons are essential in generating the inspiratory rhythm. Concurrently, we developed a mathematical model that instantiates the sigh rhythm emerges due to intracellular calcium oscillation. We then investigated the underlying network structure of the preBötC by modeling its constituent neurons using a spiking model. The network is driven by neurons that fire stochastically, but none are intrinsically rhythmic. First, we show that synaptic topology influences (1) the ability of a network to exhibit burstlets, a phenomenon that underlies inspiratory rhythmogenesis, (2) the ability of a network to trigger network excitation exogenously, and (3) the robustness of network function. We were able to recapitulate several experimental findings with our model and show that an Erdős–Rényi network with log-normally distributed synaptic weights provides simulation results that best represent experimental results. Finally, we implement intracellular calcium oscillations within the constituent neurons of the network to create the first spiking model of the preBötC that can produce burstlets and sighs. This model could help explain respiratory pathologies, such as opioid-induced respiratory depression, and provide insights into other brain rhythms.