Rhythmogenic and Premotor Functions of Dbx1 Interneurons in the pre-Botzinger Complex and Reticular Formation: Modeling and Simulation Studies

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Abstract

Breathing in mammals depends on rhythms that originate from the preBo®tzinger complex (preBo®tC) of the ventral medulla and a network of brainstem and spinal premotor neurons. The rhythm-generating core of the preBo®tC, as well as some premotor circuits, consists of interneurons derived from Dbx1-expressing precursors but the structure and function of these networks remain incompletely understood. We previously developed a cell-specific detection and laser ablation system to interrogate respiratory network structure and function in a slice model of breathing that retains the preBo®tC, premotor circuits, and the respiratory related hypoglossal (XII) motor nucleus such that in spontaneously rhythmic slices, cumulative ablation of Dbx1 preBo®tC neurons decreased XII motor output by half after only a few cell deletions, and then decelerated and terminated rhythmic function altogether as the tally increased. In contrast, cumulatively deleting Dbx1 premotor neurons decreased XII motor output monotonically, but did not affect frequency nor stop functionality regardless of the ablation tally. This dissertation presents several network modeling and cellular modeling studies that would further our understanding of how respiratory rhythm is generated and transmitted to the XII motor nucleus. First, we propose that cumulative deletions of Dbx1 preBo®tC neurons preclude rhythm by diminishing the amount of excitatory inward current or disturbing the process of recurrent excitation rather than structurally breaking down the topological network. Second, we establish a feasible configuration for neural circuits including an Erdo?s-Re¥nyi preBo®tC network and a small-world reticular premotor network with interconnections following an anti-preferential attachment rule, which is the only configuration that produces consistent outcomes with previous experimental benchmarks. Last but not least, since the performance of neuronal network simulations is, to some extent, affected by the nature of the cellular model, we aim to develop a more realistic cellular model based on the one we adopted in previous network studies, which would account for recent experimental findings on rhythmogenic preBo®tC neurons.