Role of Dbx1-derived pre-Bötzinger complex interneurons in breathing behaviors of adult mice

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Abstract

Breathing is a rhythmic motor behavior essential to sustain homeostasis and life itself in humans and all terrestrial mammals. A specialized neuronal network is responsible for generating and controlling the rhythm and pattern for breathing. The core rhythm-generating microcircuit in particular is located within a site dubbed the preBötzinger complex (preBötC). The preBötC is a heterogeneous region containing neurons with both respiratory and non-respiratory activity that express excitatory and inhibitory transmitters, peptide transmitters, and peptide receptors. More recently, preBötC neurons have been characterized by molecular genetics. The excitatory transmitter phenotype, and peptide and peptide receptors, commonly used to define the respiratory core oscillator within the preBötC are properties associated with neurons whose precursors express the embryonic transcription factor, developing brain homeobox 1 (Dbx1). Our lab, and our French colleagues, hypothesized that neurons derived from the *Dbx1*-expressing precursor cells (Dbx1 neurons) form the core microcircuit for inspiration breathing rhythm, that is, the Dbx1 core hypothesis. Evidence from many labs supports the Dbx1 core hypothesis at embryonic and neonatal stages of development. However, the role of Dbx1 neurons in adult animals remains incompletely understood. Furthermore, contemporary data suggests the portfolio of functions for brainstem Dbx1 neurons includes premotor and arousal-related functions, which casts doubt on the veracity of the Dbx1 core hypothesis. Here I investigate the role of Dbx1 neurons in adult animals with intact sensorimotor integration systems using intersectional mouse genetics to express light-responsive membrane proteins to excite or depress Dbx1 neurons while simultaneous measuring breathing. Using these light-sensitive proteins to manipulate Dbx1 neuron function to depress or stop breathing, enhance breathing, and alter the precise timing of inspiratory breaths, I offer evidence that affirms the Dbx1 core hypothesis. I conclude that Dbx1 preBötC neurons are essential for breathing and form the respiratory core oscillator in adult mice. Knowing the cellular point of origin for breathing behavior gives us a target to study the cellular and synaptic mechanisms to this key physiological behavior and provides general insight into rhythmic networks and physiological brain function.