Brain, Breathing and the Heart

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Abstract

The generation of rhythmic activity is fundamental to the brain. Rhythmicity is critical for cognition, learning and memory, the generation of sleep and wakefulness, and the generation of rhythmic motor behaviors. Breathing is a highly integrated rhythmic behavior that plays multiple roles through its interactions with the heart and various states of the brain and by controlling ventilation. Various experimental approaches led to identifying and manipulating rhythmogenic networks and neurons in the medulla that are critical for the generation of breathing. These rhythmogenic networks can reconfigure to generate different activity patterns that give rise to eupnea, sighs, and gasping. They contain excitatory and inhibitory neurons that are critical for rhythmogenesis, establishing the phase relationship and frequency of respiratory activity. Rhythmogenic networks in the brainstem interact with multiple brain areas and the heart to establish the true complexity of the breathing behavior that is essential for life.

Keywords: Brain, Rhythmicity, Breathing, Rhythmogenesis, Heart

Indian Journal of Physiology and Allied Sciences (2022); **ISSN:** 0367-8350 (Print)

Rhythmic activity is a fundamental property of life and the most characteristic feature of the brain. Most, if not all, brain regions are capable of generating rhythmic activity, and rhythms in different regions interact with each other. Rhythms generated in the thalamus and basal ganglia engage in rhythmic loops with the neocortex, and typically a given brain region generates multiple rhythms .[1,2]

McGregor *et al.,*[3] Rhythms are critical for the generation of higher brain functions, including cognition, learning and memory, sleep and wakefulness, and rhythmic motor behaviors.[4-6] A given rhythm can serve multiple functions. Breathing, a rhythmic behavior that is essential for life, is best known for its role in ventilation. However, as every yoga master knows, breathing also plays a critical role in regulating brain states[7-10] (Figure 1A). Slow breathing is used for example, to treat panic attacks.[11,12] The respiratory activity also regulates the heartbeat, and failure to coordinate breathing and the heart is associated with dysautonomia.[13-16] The heartbeat itself is a source of interoception which interacts with respiration, and even learning is affected by its phase with breathing and the heartbeat.[17-21] The sigh, a large breath with distinct mechanistic characteristics, also serves important role in regulating emotions and arousal.[8,22]

Important interactions underlying cardiorespiratory coupling occur within the lower brainstem. Respiratory activity, generated within the ventrolateral medulla, interacts with sympathetic and parasympathetic drive. These interactions are sensitive to chronic intermittent hypoxia, a condition that occurs in a variety of dysautonomia disorders, including obstructive sleep apnea, Rett Syndrome, epilepsy, Familial Dysautonomia, Sudden Infant Death Syndrome, and Mitochondrial disease.[23-26] Dysautonomia is typically characterized by decreased heart rate variability, including decreased levels of respiratory sinus arrhythmia, as well as an increased heart rate.[27] An important driver of dysautonomia are reactive oxygen species (ROS), which are generated by an imbalance of HIF1a, the pro-oxidant system, and HIF2, the anti-oxidant system.[28-31] The principles leading to dysautonomia, as discussed for chronic intermittent hypoxia, may also apply to other conditions that increase ROS production, such as lead poisoning or inflammatory diseases, such as COVID-19.

At the core of the breathing, rhythm is the ventrolateral medulla, with the pre-Bötzinger complex (preBötC) [32,33] serving as the kernel for the generation of inspiratory activity (Fig.1). The preBötC is critical for rhythmogenesis in the isolated brainstem, and lesions of this region in vivo abolishes breathing[34,35] (Figure 1B). The isolated preBötC can generate the basic respiratory rhythm (Figure 1C) that reconfigures into three distinct fictive breathing rhythms: gasping, sighing, and normal respiratory activity[36] ("eupneic activity," Fig. 1D). Critical for the generation of these rhythms are glutamatergic neurons that become active during the pre-inspiratory phase and are characterized by a peak discharge pattern during inspiration[37]. These excitatory inspiratory neurons are characterized by the transcription factor Dbx1.[38-40] Concurrently active during the inspiratory phase are inhibitory neurons that regulate the excitation level and the refractory period, characteristic of the Dbx1

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How to cite this article: Ramirez J-M. Brain, Breathing and the Heart. Indian Journal of Physiology and Allied Sciences. 2022;74(2):1-4.

Conflict of interest: None

Submitted: 17/11/2021 **Accepted:** 14/03/2022 **Published:** 15/06/2022

neurons.[41] In addition to the synaptic interactions between these excitatory and inhibitory neurons, intrinsic membrane properties contribute to rhythmogenesis.[42-46] Among these membrane, properties are the persistent sodium current and the calcium-activated non-specific cation current (ICAN) that can boost and modulate synaptic interactions and are also capable of initiating intrinsic burst activity independent of these synaptic interactions.[47] Various peptidergic and aminergic modulators play a critical role in reconfiguring and regulating the respiratory rhythm to orchestrate eupneic, sighing and gasping activity.[48-50]

The preBötC interacts with other rhythmogenic regions, the post-inspiratory complex (PiCo) [51] and the parafacial region (pFRG) that are critical for generating post-inspiratory activity and active expiration, respectively.[52,53] While glutamatergic mechanisms within these "oscillators" are critical for rhythmogenesis, the phase-dependent interactions between these regions depend on inhibitory mechanisms.[51] However, the concept that the respiratory rhythm is generated by three distinct and interacting rhythmogenic oscillators [54] or by distinct compartments have also been proposed,[55-57] is certainly a simplification. Recent evidence suggests that the respiratory network is spatiotemporally dynamic. Dbx1 neurons e.g., extend along the entire ventrolateral medulla, and rhythmogenic properties contributing to inspiratory activity extend beyond the preBötC. Indeed, as the respiratory network reconfigures into gasping, areas rostral to the preBötC are recruited,[58] which is consistent with the observation that lesioning, specifically, the preBötC in vivo eliminates breathing but not gasping.[34] During eupneic breathing, vagal afferents inhibit these rostral areas, reducing the inspiratory rhythm's refractory period and enabling the respiratory network to generate a faster eupneic rhythm. Lesioning of vagal afferents leads to the disinhibition of these rostral areas, which expands the respiratory network, increasing the refractory period and significantly slowing respiratory activity.[41,58] Thus, breathing in the absence of vagal afferents is too slow for adequate ventilation and gas exchange, and the organism succumbs.

While the medullary interactions described above are critical for generating the basic respiratory rhythms that give rise to the different activity patterns like gasping, sighing, and eupneic activity, breathing behavior is much more than these basic rhythms as described at the beginning of this article. To turn these basic rhythms into breathing behavior with all its complexity and plasticity depends on numerous interactions. The interplay between various regions in the medulla is critical for the sensorimotor integration of the respiratory rhythm, for the coordination

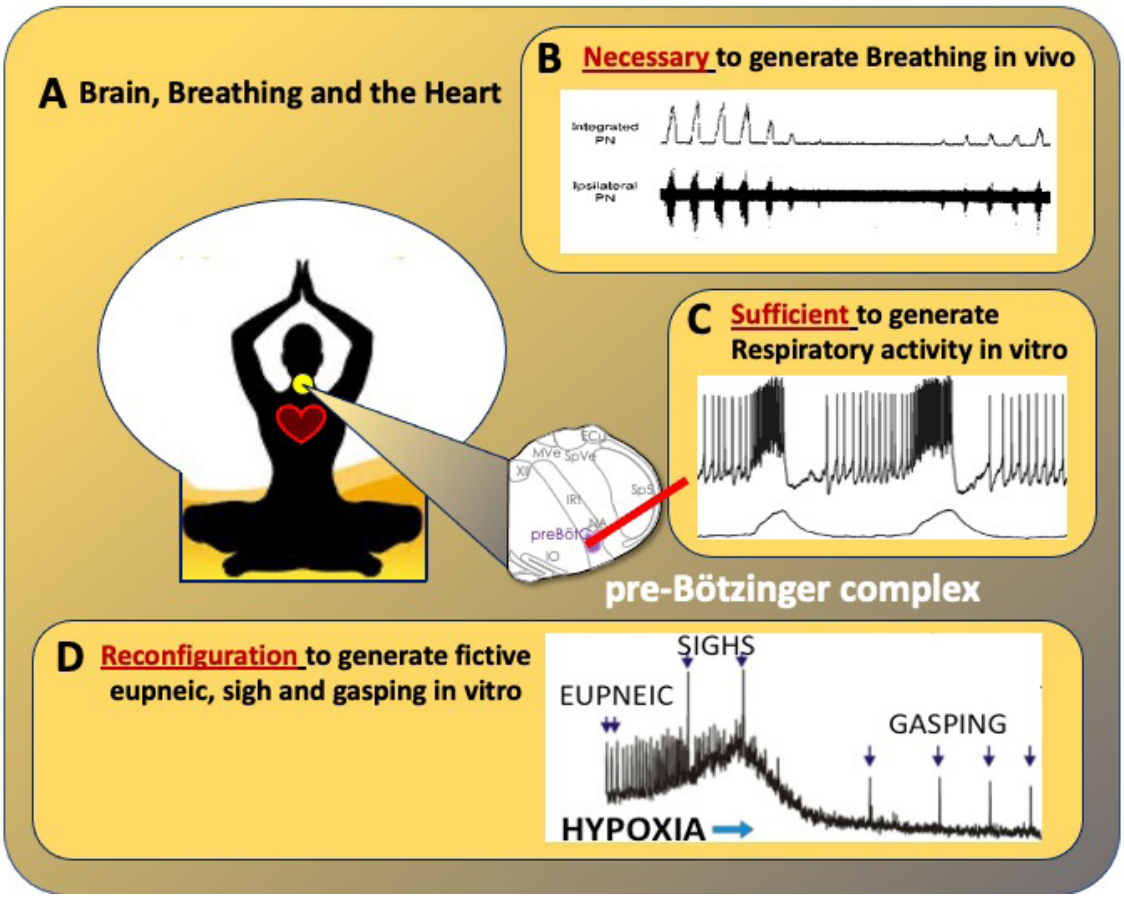

Figure 1: Critical roles played by Yoga in regulating brain states.

and reconfiguration of breathing during swallowing, coughing, and sneezing, and for the coordination with the sympathetic and parasympathetic control of the heartbeat and blood pressure. The interactions between the pons, the midbrain, and the forebrain are critical for the emotional and behavioral control of breathing, the state-dependent regulation of breathing during sleep and wake cycle, and for the arousal response. Thus, while breathing may seem like a simple rhythm that consists of inhalation and exhalation, it is a fully integrated behavior within our body and mind. Its rhythmic activity is integrated with other rhythmic activities generated within the central nervous system, and it is also integrated with rhythmic activities outside the brain, like the heart. This integration is critical for an organism to thrive and adapt to the continuously changing metabolic and environmental challenges. Disintegration and de-regulation of these interactions give rise to numerous diseases that are characterized by dysautonomia. Understanding these interactions at the cellular level, but also in a wholistic manner at the systems level will be important to treat and prevent dysautonomia effectively. While unraveling the complexity of these interactions is daunting, it is also an opportunity. By healing breathing at different levels of integration, it is possible to exert an influence on the entire body, something that the yoga masters have clearly understood. As a physiologist, the integration of systems and cellular levels has always been a major goal. This goal has become attainable with the advent of novel transgenic, molecular, and systems-level technologies. This integrative understanding will provide important insights into breathing and lead to a better understanding of the brain and its fundamental property to generate, coordinate and integrate rhythmic activities.

Acknowledgement

This article was funded by grants from the National Institute of Health R01 HL151389, R01 HL126523, R01 HL144801, P01 HL144454.

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