Commentaries on Viewpoint: Initiating inspiration outside the medulla does produce eupneic breathing

WHY SHOULD IT NOT?

TO THE EDITOR: As the title of this Viewpoint (3) states, “Initiating inspiration outside the medulla does produce eupneic breathing.” My view is why should it not? Although many experiments have explored the cortical-spinal pathway to phrenic motoneurons, producing the idea that behavioral and metabolic respiratory demands compete at the spinal respiratory motor neurons (5), there is also evidence that medullary-generated breaths can be modified from structures external to the medulla. Numerous areas of the brain including the cortex have medullary connections (2). For example, brief stimuli applied to the central gray substance of the midbrain and the ventral hippocampus can initiate a phase reversal in respiration from expiration to inspiration (4). These recordings of medullary neurons and phrenic activity show that, after the phase is switched from expiration to inspiration, the inspiration initiated within the medulla is similar in strength and duration to previous inspirations. That the discharge of these medullary neurons is under chemoreflex control has been recognized for many years (1).

So, these brief stimuli from outside the medulla simply reset the phase of the medullary respiratory rhythm generator, which continues to operate normally, coupling breathing to metabolic needs via chemoreflex control as the Viewpoint author found.

REFERENCES


WHAT IS THE ROLE OF BRAIN STEM NEURONS IN EUPNEIC BREATHING?

TO THE EDITOR: Breathing is an important motor behavior that begins in utero and continues virtually uninterrupted from birth until death. It is originated via neural mechanisms in the brain stem and it is regulated by a complex system that includes chemical feedback (2). The neural mechanisms of breathing must be stable yet responsive to challenges affecting O2, CO2, and pH levels in the body. It is also important to consider that the central nervous system highly contributes to breathing automaticity by various means including multiple oscillator sites and multiple mechanisms for oscillation (2). In the present Viewpoint, Dr. Haouzi (3) discussed the observation that breathing can display the same essential regulatory properties whether generated outside or within the brain stem. The literature has reported few examples showing breathing rhythmicity outside the brain stem (1, 4). These reports reveal that breathing activity could be locked to locomotor output of the limb nerves, suggesting that breathing output is entrained by locomotor rhythm rather than by the presence of an endogenous spinal respiratory oscillator. Although some evidence indicates that brain regions outside the brain stem play a role in the breathing control, we conceive that this paradigm has to be taken into consideration to unravel the complexity of brain stem mechanisms, especially in the pre-Botzinger complex, to control and generate eupneic breathing.

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RESPIRATORY ACTIVITY FOR AUTONOMIC BREATHING AND FOR ADJUSTING METABOLISM IS REGULATED BY THE MEDULLA

TO THE EDITOR: Respiration can voluntarily change by activation of the cerebral cortex, and involuntarily change by activation of the limbic system. Haouzi (1) noted that cortical activation induces respiratory changes, especially in the motor areas involved in voluntary breathing as well as during speech and phonation. Animal studies have demonstrated that there are two different pathways for metabolic and volitional breathing, and cortical projections to the brain stem have been found to modify metabolic breathing.

In addition to this high level of cooperation between above separate two systems, the limbic structure involved in respiratory changes (2). In the awake state, respiration is greatly influenced by various emotional stimuli. An increase in respiratory frequency (fR) with an increase in anxiety occurs at the same time as activation of the amygdala (AMG) (3, 4). A connection was found between the AMG and lower brain stem using a limbic-brain stem-spinal cord preparation in newborn rats (5). Spontaneous rhythmic activity was initially reported in the piriform cortex, and it then propagates mediolaterally to terminate in the lateral AMG. This piriform-limbic rhythmic activity is associated with inspiratory activity in the medulla. In human study, fR increase coactivates the AMG during negative emotions with unchanged VT and this results in decrease of end-tidal CO2 (3). The limbic breathing overrides spontaneous breathing and maintaining homeostasis of the body. Thus this limbic breathing system might affect autonomic and volitional breathing.
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INTEGRATION OF VOLITIONAL AND SPONTANEOUS BREATHING CONTROL WITHIN THE BRAIN STEM

TO THE EDITOR: The interaction between volitional and spontaneous respiratory control is not yet understood. There is compelling evidence from animal and human studies that the two control pathways integrate at the level of the brain stem. In awake cats trained to behaviorally terminate breathing, medullary neuronal activity occurs in synchrony with behavioral respiratory responses (5), suggesting a cortical influence on brain stem respiratory control. In patients with “locked-in syndrome” caused by corticospinal and corticobulbar tract damage at the level of the pons, volitional control of breathing is absent, while spontaneous breathing and ventilatory responses to CO2 remain intact (2). These observations support the notion that the volitional control pathway bypasses brain stem areas generating spontaneous breathing. However, locked-in patients have reduced variability in resting breathing compared with controls (2), possibly due to an absence of corticobulbar input from supra-brain stem structures. Additionally, the emotional influence on breathing, originating in the limbic system, is maintained in locked-in patients (2). These findings, together with results from functional imaging studies on breath holding and volitional hyperventilation (3, 4) point toward integration of volitional and spontaneous respiratory control pathways at the level of the brain stem. Studying the respiratory control pathways in isolation from one another in awake humans is clearly very difficult. Haouzi presented an interesting hypothesis that initiation of eupneic breathing can occur without input from brain stem respiratory control centers (1) but until the neurophysiological basis of volitional respiratory control is established, the role of the brain stem in initiating eupnea can not be dismissed.

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NON-MEDULARY STRUCTURES MAY SCULPT INSPIRATORY MOTONEURONAL OUTPUT

TO THE EDITOR: The Viewpoint article (3) exposes the challenge for ventilatory control systems—how is isocapnia maintained when ventilation is initiated spontaneously or by volitional or emotional stimuli? What does the pontomedullary central pattern generator (CPG) do under these different circumstances? “Cooperation” between these ventilatory modes may involve not simply termination of inspiration at a volume and time that maintain isocapnia, but also the neural structures that distribute inspiratory drive to the obligatory inspiratory motoneurons so as to ensure efficient matching between neural drive and mechanical action (1, 2). Where and how this matching is translated into the outputs from inspiratory motoneuron pools is unknown (1, 2). Recently, we monitored differential drive to parasternal intercostal muscles before and after the seamless transition between spontaneous (CPG driven) inspiration (recorded surreptitiously) and highly volitional inspiration, which tracked the profile of tidal inspiratory volume (4). The pattern of output across the different parasternal intercostal motoneuron pools was strikingly similar under the two conditions. Given the lack of excitatory drive between the motor cortex and pontomedullary respiratory centers and the normal differential distribution of inspiratory intercostal drive given thoracic spinal stimulation in dogs (5), we propose that distribution of inspiratory drive is coordinated via networks of propriospinal neurons.

With sequential evolution of spinal then bulbar then cortical drives to the motoneurons acting on the body (later chest) wall, development of efficient spinal networks for coordination of involuntary respiratory and voluntary truncal movements seems essential. Such networks would be a final common pathway for multiple sources of respiratory drive.

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