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Review

Clinical consequences of altered chemoreflex control☆

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ABSTRACT

Control of ventilation dictates various breathing patterns. The respiratory control system consists of a central pattern generator and several feedback mechanisms that act to maintain ventilation at optimal levels. The concept of loop gain has been employed to describe its stability and variability. Synthesizing all interactions under a general model that could account for every behavior has been challenging. Recent insight into the importance of these feedback systems may unveil therapeutic strategies for common ventilatory disturbances. In this review we will address the major mechanisms that have been proposed as mediators of some of the breathing patterns in health and disease that have raised controversies and discussion on ventilatory control over the years.

1. Introduction

Ventilation is a rhythmic act that maintains the oxygen (O_2) and carbon dioxide (CO_2) in the arterial blood and tissues within levels required for survival. The automatic process of breathing originates from the respiratory circuits in the pons and medulla: the dorsal respiratory group within the caudal third of the nucleus of the tractus solitarius (cNTS), the ventral respiratory column (VRC), and the pontine respiratory group (Alheid and McCrimmon, 2008). The cNTS is the principal site of sensory input from pulmonary and airway afferents and from peripheral chemoreceptors and contains mainly inspiratory neurons. Respiratory rhythm generation occurs mainly in the rostral VRC and the activity of caudal VRC modulates the amplitude of respiratory motor output. In the caudal VRC, the ventral respiratory group (VRG) is subdivided into rostral and caudal VRG based on the prominence of inspiratory and expiratory neurons respectively. The rostral VRC contains the Botzinger and preBotzinger complex, the retrotrapezoid nucleus (RTN), and the parafacial respiratory group. The preBotzinger complex is considered essential for inspiratory rhythm generation (Alheid and McCrimmon, 2008; Ramirez, 2011). The existence of a separate expiratory rhythm generator has been proposed in the region of the RTN/parafacial group (Janczewski and Feldman, 2006). RTN neurons serve as central chemoreceptors and the RTN appears to play a role in the integration of central and peripheral chemoreceptor afferents. The pontine respiratory group contains neurons of the parabrachial complex and the Kolliker–Fuse nucleus with projections to the VRC and areas of the NTS (Alheid and McCrimmon, 2008). The pneumotaxic center in the upper pons inhibits inspiration and damage in this area results in large tidal volumes and bradypnea (Roca and Malhotra, 2010). The central controller provides the major source of input to spinal motoneurons activating the respiratory muscles.

The respiratory center is modulated by chemoreceptors, cells responsive to the chemistry of the fluid around them. Central chemoreception is mediated by the simultaneous effects of CO_2 via proxy of changes in hydrogen ion (H^+) concentration on multiple types of acid sensitive neurons, as well as glia and vascular cells (Guyenet et al., 2010). It is still unclear if chemoreception relies on a few cells or is widely distributed throughout the brain. The combination of sites that determine chemoreception could vary by arousal state, age and gender (Nattie and Forster, 2010). Several acid-sensitive ion channels on a given neuron may be involved. The RTN contains the most thoroughly characterized group of chemoreceptor cells although the molecular mechanism of their activation is still unknown. Their CO_2 sensitivity seems to rely on three mechanisms: a cell autonomous sensitivity to acid, a paracrine effect mediated by surrounding glial cells and inputs from peripheral chemoreceptors and possibly other central acid sensitive neurons. Other potential chemoreceptor sites include the serotonergic neurons of the raphe, the noradrenergic neurons of the locus coeruleus, NTS neurons and orexinergic neurons (Guyenet et al., 2010, 2012). The peripheral chemoreceptors are located in the carotid bodies at

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the bifurcation of the common carotid arteries and the aortic bodies near the arch of the aorta (mainly relevant in nonhuman species). They are sensitive to partial arterial oxygen pressure (PaO_2) and to a lesser extent to arterial carbon dioxide partial pressure ($PaCO_2$) and pH changes. The response of the peripheral chemoreceptors to $PaCO_2$ is more rapid than that of the central ones. The interactions between central and peripheral chemoreceptors are still debated, but a hyperadditive model has been proposed whereby the gain on the former chemoreceptors can amplify the gain on the latter ones, and vice versa (Smith et al., 2010). Stimulation of the peripheral chemoreceptors during acute hypoxia is accompanied by sympathoexcitation initiated at the carotid bodies. Repeated intermittent hypoxia increases chemosensitivity and sympathetic activity during acute hypoxia (Lusina et al., 2006). The observed linkage between the sympathetic and hypoxic ventilatory response can be secondary to a common central control region or separate control centers modulated to a similar degree, but the causal pathways are still being defined. The rise in ventilation in response to increases in $PaCO_2$ is approximately linear, but the sensitivity to changes in PaO_2 is very nonlinear; the response to hypoxia is more vigorous at lower levels of PaO_2. Moreover, the effects of hypercapnic and hypoxic stimuli are typically multiplicative; that is, the combined response can exceed the sum of each stimulus given separately.

Secondary modulators also affect ventilation: voluntary control from the cerebral cortex through the corticospinal and corticobulbar tracts, the limbic system and hypothalamus can affect breathing (Evans, 2010; Evans et al., 1999; Kc and Dick, 2010; Nattie and Li, 2012; Shea, 1996). Receptors in the lung include stretch, irritant and J receptors and bronchial C-fibers (Kubin et al., 2006). Finally nose and upper airway receptors, joint and muscle proprioceptors, arterial baroreceptors, pain and temperature can all influence the pattern of breathing (Roca and Malhotra, 2010). During wakefulness a tonic input from various brainstem centers is present (so-called wakefulness stimulus) and is suppressed during sleep (Bulow, 1963; Fink, 1961). Chemosensitivity is also diminished during sleep (McKay and Morrell, 2010; Roca and Malhotra, 2010). Both the hypercapnic and hypoxic ventilatory responses are blunted in stages 2 and 3/4 compared to wakefulness and further decreased in REM sleep (Douglas et al., 1982a,b; Stephenson et al., 2000).

Control of breathing encompasses a wealth of mechanisms that dictate the behavior of the respiratory system at rest, under physiological challenges, and in disease. In this review we highlight several examples of interesting breathing patterns/findings in health and disease that have raised controversies and discussion over recent years (Table 1).

1.1. The concept of loop gain

Several ventilatory control disorders manifest as oscillatory fluctuations in ventilation. The propensity for ventilation to oscillate can be encapsulated by the engineering concept of *loop gain*, which describes the overall stability of the feedback system controlling ventilation. To employ this concept, we consider the ventilatory control system as characterized by three main components: (a) the 'controller gain', which is the response as a change in ventilation per change in unit $PaCO_2$ or PaO_2; (b) the 'plant gain', which can be expressed as the change in $PaCO_2$ or PaO_2 per unit change in ventilation; (c) the circulation delay between the lungs and the peripheral and central chemoreceptors (Cherniack and Longobardo, 2006) (Fig. 1). If we consider a disturbance to the system, i.e. a transient hyperventilation, this disturbance will lower $PaCO_2$ (depending on the plant gain), and after a delay, the controller will respond to the disturbance with a corrective action (depending on controller gain). Whether oscillations will develop or not, depends on the ratio of the magnitude of the corrective action to the magnitude of the disturbance; this ratio is called "loop gain" (LG) (Khoo et al., 1982).

LG is the product of controller gain and plant gain and determines the stability of the control system. In an inherently stable system, LG is less than 1, i.e. the response to the initial perturbation is smaller in magnitude than the initial insult and the effect of a transient disturbance is eventually suppressed. If LG is greater than 1, the feedback loop will magnify the initial insult and an oscillation will continually grow in amplitude until periodic central apnea (cessation of breathing effort) or 'periodic breathing' is observed. An important subtlety is that oscillations will grow or decay at a frequency called the *natural frequency* (~1 cycle/min in heart failure; ~3 cycles/min in adults at high altitude) that depends on the circulatory delay: thus, LG is examined at this frequency to reflect the propensity to oscillate (Khoo et al., 1982). It is at this natural frequency that the system responds to a sinusoidal disturbance with a response precisely "in phase" with the disturbance, positively reinforcing it to produce periodic breathing if LG is >1; if LG is <1 then transient disturbances are damped away and the system is considered to be stable. This mathematical approach to respiratory control has provided important insight to respiratory instability as exemplified later in this review (Edwards et al., 2013).

2. Cheyne–Stokes respiration in heart failure

Perhaps the most common expression of ventilatory control system instability is Cheyne–Stokes breathing (CSB), characterized by cyclic crescendo–decrescendo changes in ventilation with

Table 1
Proposed mechanisms and treatment of breathing patterns associated with altered chemoreflex control.

Breathing pattern	Mechanism	Treatment
Cheyne–Stokes in heart failure	Increased chemosensitivity to CO_2, reduced proximity of $PaCO_2$ to apneic threshold, circulatory delay	Heart failure medication optimization, PAP devices, heart transplantation
High altitude periodic breathing	Increased sensitivity to hypoxia, increased carotid body chemosensitivity, augmented neural input processing, left shift of the CO_2 response	Gradual ascent, oxygen, acetazolamide
Obstructive sleep apnea	Compromised upper airway anatomy, upper airway muscle dysfunction, high loop gain	Weight loss, CPAP devices, oxygen, acetazolamide
Obesity hypoventilation syndrome	Reduced respiratory system compliance, increased work of breathing, high upper airway resistance, lower ventilatory drive, leptin resistance	Weight loss, bilevel or CPAP devices
Oxygen induced hypercapnia	Depression of central chemosensitivity to CO_2, increased physiological dead space, Haldane effect, sleep	Oxygen delivery titrated to an oxygen saturation of 87–92%; bi-level PAP
Exercise hyperpnea	Mechanoreceptors, nociceptors and metaboreceptors in exercising muscles, breath by breath oscillations in $PaCO_2$ and PaO_2, central parallel stimulation of ventilation and exercise, ventilatory–circulatory coupling	

CO_2 = carbon dioxide; $PaCO_2$ = partial arterial pressure of carbon dioxide; PaO_2 = partial arterial pressure of oxygen; PAP = positive airway pressure.

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