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Drawing breath without the command of effectors: The control of respiration following spinal cord injury

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ABSTRACT

The maintenance of blood gas and pH homeostasis is essential to life. As such breathing, and the mechanisms which control ventilation, must be tightly regulated yet highly plastic and dynamic. However, injury to the spinal cord prevents the medullary areas which control respiration from connecting to respiratory effectors and feedback mechanisms below the level of the lesion. This trauma typically leads to severe and permanent functional deficits in the respiratory motor system. However, endogenous mechanisms of plasticity occur following spinal cord injury to facilitate respiration and help recover pulmonary ventilation. These mechanisms include the activation of spared or latent pathways, endogenous sprouting or synaptogenesis, and the possible formation of new respiratory control centres. Acting in combination, these processes provide a means to facilitate respiratory support following spinal cord trauma. However, they are by no means sufficient to return pulmonary function to pre-injury levels. A major challenge in the study of spinal cord injury is to understand and enhance the systems of endogenous plasticity which arise to facilitate respiration to mediate effective treatments for pulmonary dysfunction.

1. Introduction

Breathing is essential to life. From birth, blood oxygen, carbon dioxide, and pH levels are regulated and maintained through respiration in all states of behaviour and consciousness, including cortical dysfunction. The homeostatic regulation of pulmonary function originates in the respiratory control centres located in the brain stem such as the central pattern generator (CPG). Through pathways which descend through the spinal cord, the frequency and firing of effectors (the respiratory muscles) are determined. The changes in ventilation evoked through controlled muscle contraction feedback to the respiratory control centres to enable continuous regulation. However, this critical mechanism of respiratory homeostasis is not autonomic but automatic. While it can be described as a static process of blood gas and pH regulation, the endogenous plasticity inherent in the respiratory motor system enables it to be a dynamic series of processes. For example, different neurons and neurotransmitters are activated in the respiratory control centres during the inspiratory processes of eupnea, sighs, and gasping (Lieske and Ramirez, 2006; Garcia et al., 2011; Dunmyre et al., 2011); respiratory muscle activity is tightly coordinated with, and altered for, speech and swallowing; and, following feedback from chemoreceptors, expiration during exercise becomes an active rather than passive process.

Damage to any part of the homeostatic system that controls respiration can cause pulmonary dysfunction that is detrimental to life. This can occur following spinal cord injury (SCI) where the descending pathways which innervate the respiratory muscles are severed or retract. The brainstem can no longer evoke control over, or receive feedback from, all of its effectors. Respiratory complications occur in 36–83% of cases with acute SCI (Carter, 1987; Jackson and Groomes, 1994; Lanig and Peterson, 2000; Claxton et al., 1998; Lemons and Wagner, 1994; Winslow and Rozovsky, 2003) and pulmonary dysfunction is the leading cause of morbidity and mortality at both acute and chronic stages (Claxton et al., 1998; Jackson and Groomes, 1994). The resulting weakness or spasticity of respiratory muscles can cause reductions in vital and inspiratory capacity, inability to clear bronchial secretions or cough, pneumonia, septicemia, atelectasis, and pulmonary embolism (Winslow and Rozovsky, 2003; Lemons and Wagner, 1994; Reines and Harris, 1987; Schmitt et al., 1991; Vale et al., 1997). Indeed, many sufferers of SCI experience some degree of hypoxaemia, which can intensify ischemia following acute trauma (Ledsome and Sharp, 1981; Lu et al., 2000; McMichan et al., 1980).

The exact nature of pulmonary dysfunction following SCI is dependent upon the level of trauma, with high cervical injuries

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causing a loss of innervation to more respiratory muscles than that caused by damage to the lower thoracic cord (see Section 3.1). However, without the correct functioning of respiratory muscles, pulmonary functions are dramatically impaired following trauma to the spinal cord. In this review, we will summarise the recent developments in understanding how respiration is controlled following spinal trauma. In looking at the brainstem respiratory control centres, motoneurons and the respiratory muscles, the systems and endogenous mechanisms of plasticity evoked to attempt the maintenance of respiratory homeostasis will be described and new hypothesis relating to these processes will be related.

2. Brainstem respiratory control centres affecting motoneuron activity

2.1. Organization of the medullary regions controlling respiration

The generally accepted model for the organization and interaction of medullary centres of homeostatic respiratory control extends from the pons to the caudal extent of the medulla (Fig. 1) and is reviewed by Rybak et al. (2007) and Smith et al. (2007). Briefly, post-inspiratory/expiratory neurons occur in the Bötzinger Complex (BC); pre-inspiratory/inspiratory and early inspiratory neurons populate the pre-Bötzinger Complex (pre-BC); while ramp-inspiratory pre-motor bulbospinal and inhibitory early-inspiratory neurons exist in the rostral ventral respiratory group (rVRG). Brainstem areas which are able to mediate excitatory respiratory drive include the pons, RTN (retrotrapezoid nucleus), and raphe which modulate the core pattern generation produced in the BC and pre-BC. The activity is further modulated from areas of peripheral respiratory feedback. For example, the nucleus tractus solitarii (NTS) receives sensory feedback from the lungs, carotid body, and respiratory muscles, and the ventral lateral medulla (VLM) mediates the activity of baroreceptors (reviewed in Molkov et al., 2013; Baekey et al., 2010). The interaction of all the excitatory and inhibitory neuronal populations, combined with input from other medullary areas, produce the neuronal oscillations typical of respiration. These centres are connected to the rVRG which projections innervate the motorpools for many of the respiratory muscles, for example the phrenic motor neurons which innervate the diaphragm.

2.2. Medullary regions controlling respiratory pattern generation

Models of homeostatic respiratory pattern generation define three phases of rhythm which occur under numerous experimental conditions and include inspiratory, post-inspiratory or early-expiratory, and late-expiratory (Schwarzacher et al., 1991). These models typically assume that the physiological substrate of the respiratory CPG is located in the medulla with inspiratory neurons located in the preBC, active expiration governed by the BC, while other respiratory neurons exist in the VLM (Fig. 1; Dutschmann and Dick, 2012; Lindsey et al., 2012; Smith et al., 2013). The pattern of respiratory activity is thought to arise from the interactions between these areas and the integration of feedback from respiratory efferents. The medulla is not physically altered immediately following SCI, although secondary processes and endogenous plasticity may cause modification in the weeks to months following trauma (Zimmer and Goshgarian, 2007). However, the areas of the brainstem which generate respiratory rhythm prior to injury are typically assumed to perform a similar function post injury. This is not to say that the control of respiration following SCI is homeostatic. While the medullary control circuitry still operates, the interaction between these homeostatic circuits and their effectors is disrupted after SCI (see Sections 3 and 4) meaning that respiration is then non-homeostatic. Nonetheless, the mechanism of respiratory rhythm generation during eupnea is briefly described below. Evidence is then presented to suggest that, post injury, endogenous plasticity may evoke the possibility of modification to this system.

It is generally agreed that the preBC is necessary and sufficient for inspiratory motor activity (Smith et al., 1991). Indeed, with only this area intact inspiration rhythm patterns are possible following *in vivo* transection injuries (Janczewski and Feldman, 2006). Further, hyperpolarization of these neurons generates prolonged apnoea (Tan et al., 2008). There remains some controversy concerning exactly how an excitatory rhythmic signal is generated within these neurons, a conclusion which seems dependent upon the model used to obtain data. It is generally accepted that glutamatergic interneurons generate rhythm in the preBC (Funk et al., 1993; Wallen-Mackenzie et al., 2006). However, whether this is caused by a population of pacemaker neurons or due to the interaction of neurons that can be synaptically triggered to generate bursting activity is unknown. In slice preparation, approximately 5–23% of preBC inspiratory neurons within neonates generate pacemaker activity (Pena et al., 2004; Morgado-Valle et al., 2010), although whether

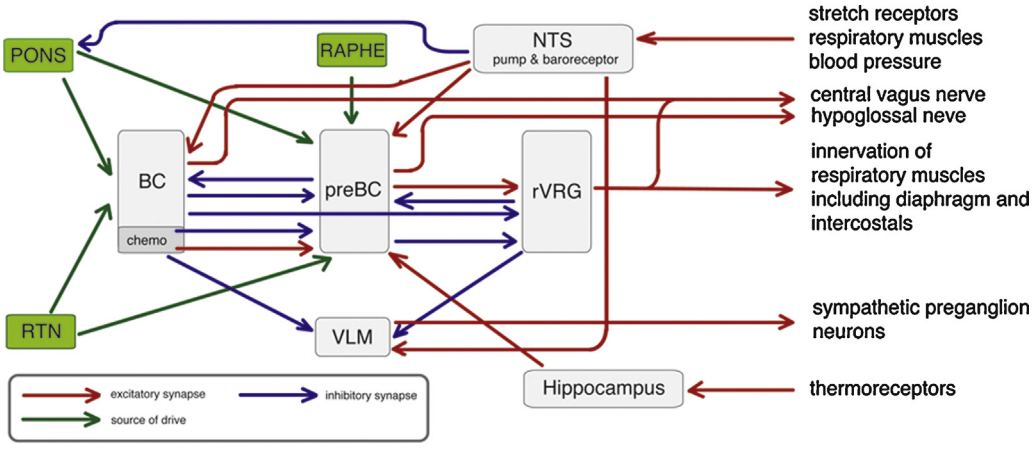

Fig. 1. A simplified schematic of the medullary respiratory motor system network. Inhibitory connections are shown in blue while excitatory connections are shown in red. A number of areas of tonic excitatory drive are illustrated in green (for a full list see Smith et al., 2007). VLM = ventro lateral medulla; rVRG = rostral ventral respiratory group; NTS = nucleus tractus solitarii; BC = Bötzinger Complex; preBC = pre-Bötzinger Complex; chemo = area of the BC with chemoreceptors which can modulate respiratory rhythm; RTN = retrotrapezoid nucleus.