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Review

Similarities and differences in mechanisms of phrenic and hypoglossal motor facilitation☆

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ABSTRACT

Intermittent hypoxia-induced long-term facilitation (LTF) is variably expressed in the motor output of several inspiratory nerves, such as the phrenic and hypoglossal. Compared to phrenic LTF (pLTF), less is known about hypoglossal LTF (hLTF), although it is often assumed that cellular mechanisms are the same. While fundamental mechanisms appear to be similar, potentially important differences exist in the modulation of pLTF and hLTF. The primary objectives of this paper are to: (1) review similarities and differences in pLTF and hLTF, pointing out knowledge gaps and (2) present new data suggesting that reduced respiratory neural activity elicits differential plasticity in phrenic and hypoglossal output (inactivity-induced phrenic and hypoglossal motor facilitation, iPMF and iHMF), suggesting that these motor pool-specific differences are not unique to LTF. Differences in fundamental mechanisms or modulation of plasticity among motor pools may confer the capacity to mount a complex ventilatory response to specific challenges, particularly in motor pools with different "jobs" in the control of breathing.

1. Introduction

The respiratory control system coordinates the regular, rhythmic contraction of multiple respiratory muscles to achieve one of the most fundamental of mammalian behaviors: breathing. The networks controlling the respiratory musculature are not static, but adapt neural output to meet the challenges of an ever-changing organism. One mechanism whereby the respiratory control system adapts breathing is through plasticity, a change in system performance based on experience (Mitchell and Johnson, 2003). While plasticity may occur at multiple levels in the neural networks underlying breathing (Mitchell and Johnson, 2003), plasticity within or near respiratory motor pools is a fundamental property of respiratory control.

The most extensively investigated forms of respiratory motor plasticity are those that elicit long-lasting increases in phrenic burst amplitude. Recently, it has become clear that phenotypically similar increases in phrenic burst amplitude can be elicited by multiple stimuli through distinct cellular pathways (Dale-Nagle et al., 2010a,b; Golder et al., 2008; Hoffman and Mitchell, 2011; MacFarlane et al., 2011; Mahamed et al., 2011; Tadjalli et al., 2010; Zhang et al., 2004). Thus, the term "phrenic motor facilitation" (pMF) has been coined to describe a prolonged increase in phrenic burst amplitude regardless of the inducing stimuli or the evoked cellular pathway (Dale-Nagle et al., 2010a). The most frequently studied form of pMF is phrenic long-term facilitation (pLTF) following acute exposure to intermittent hypoxia (AIH). Rapid progress has been made over the last decade in understanding the mechanisms giving rise to pLTF (see Mitchell and Terada, 2011; Dale-Nagle et al., 2010a,b for review).

AIH-induced LTF is also expressed in the motor output of other respiratory-related nerves, including the hypoglossal (Bach and Mitchell, 1996), glossopharyngeal (Cao et al., 2010) and intercostal (Fregosi and Mitchell, 1994). In comparison to pLTF, far less is known about the mechanisms of LTF in other motor pools, although it is generally assumed that cellular mechanisms are the same (Baker-Herman et al., 2010; Cao et al., 2010; Feldman et al., 2003;

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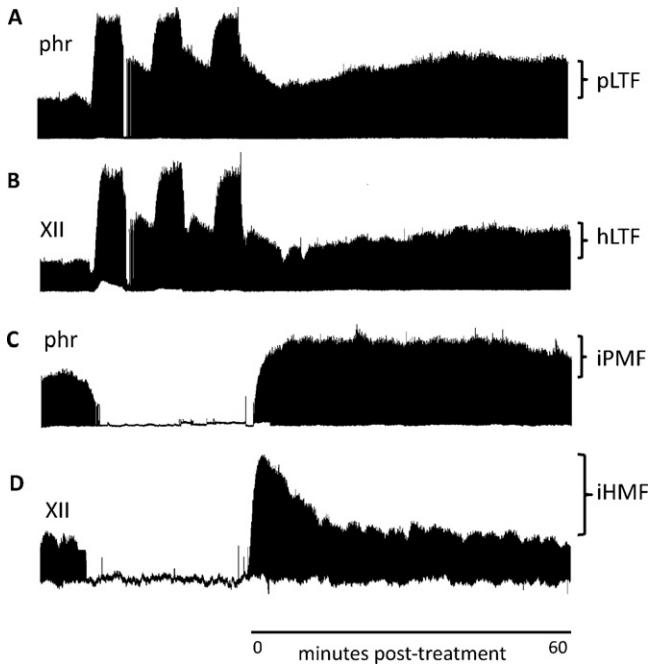

Fig. 1. Intermittent hypoxia and a prolonged, hypocapnia-induced neural apnea elicit different forms of phrenic and hypoglossal motor plasticity. (A and B) Representative compressed integrated phrenic (A) and hypoglossal (B) neurograms measured before, during and for 60 min after 3, 5 min episodes of hypoxia (11% O_2), separated by a 5 min return to baseline conditions. A phenotypically similar LTF is present in both phrenic (pLTF) and hypoglossal (hLTF) motor output, with a progressive increase in burst amplitude from baseline levels that develops slowly over the course of an hour following intermittent hypoxia exposure. (C and D) Representative compressed integrated phrenic (C) and hypoglossal (D) neurograms measured before, during and for 60 min after a 30 min neural apnea in pump-ventilated rats. Upon restoration of respiratory neural activity, phrenic burst amplitude is immediately elevated above baseline, and remains above baseline levels for at least 1 h, indicating a long-lasting inactivity-induced phrenic motor facilitation (iPMF). By contrast, hypoglossal burst amplitude is transiently elevated above baseline levels upon restoration of respiratory neural activity, indicating that inactivity-induced hypoglossal motor facilitation (iHMF) is only briefly expressed.

Mahamed and Mitchell, 2007; Wilkerson and Mitchell, 2009). However, accumulating evidence suggests that, although LTF in different respiratory motor pools is fundamentally similar, there are also interesting and important mechanistic differences that may be appropriate for their respective physiological roles. For example, LTF in upper airway motor activity (e.g., hypoglossal) is expected to affect upper airway resistance and patency in contrast to LTF of respiratory pump muscle activity (e.g., phrenic and intercostal), which would act to increase inspiratory efforts.

One primary purpose of this review is to compare LTF in a motor pool innervating a respiratory pump muscle (phrenic/diaphragm; Fig. 1A) with a motor pool innervating muscles contributing to the regulation of upper airway patency (hypoglossal/tongue; Fuller, 2005; Fig. 1B), and to point out gaps in current knowledge. We define phrenic and hypoglossal LTF (pLTF and hLTF, respectively) as increased integrated nerve burst amplitude following AIH because available evidence suggests that: (1) burst amplitude LTF arises from mechanisms operating in or near the respiratory motor pool, whereas respiratory frequency LTF likely arises from mechanisms operating in the brainstem networks generating respiratory rhythm or in afferent pathways leading to those rhythm-generating centers (Baker-Herman and Mitchell, 2008; Blitz and Ramirez, 2002; Powell et al., 1998); and (2) profound mechanistic differences can exist between AIH-induced increases in burst amplitude and burst amplitude facilitation elicited by other stimuli, such as pulses of serotonin receptor agonists (Hoffman and Mitchell, 2011; MacFarlane et al., 2011), adenosine receptor agonists (Golder et al., 2008), vagal feedback (Tadjalli et al., 2010; Zhang et al., 2003, 2004) or reduced respiratory neural activity (Baker-Herman, 2009; Mahamed et al., 2011). As a general term for burst amplitude plasticity, we follow the lead of Dale-Nagle et al. (2010a) by using the terms phrenic motor facilitation and hypoglossal motor facilitation (hMF). Only when the motor facilitation is caused by AIH *per se* will we refer to it as long-term facilitation or LTF (Dale-Nagle et al., 2010a) (Table 1).

A second purpose of this review is to discuss a recently described form of plasticity elicited by a prolonged neural apnea: inactivity-induced facilitation (Mahamed et al., 2011). We present limited new data suggesting that burst amplitude facilitation induced by reduced respiratory neural activity differs between phrenic and hypoglossal motor outputs, similar to AIH-induced LTF. Thus, the concept that plasticity in the strength of respiratory motor output is differentially and locally regulated at the level of the motor neuron pool (or motor nucleus) may be a common feature of many forms of respiratory plasticity. An understanding of mechanistic differences in plasticity among respiratory motor outputs that create a breath is critical to understand the physiological significance of respiratory plasticity. Further, a detailed understanding of differences in the capacity for plasticity in different respiratory motor pools may offer unique opportunities as we attempt to target key molecules to selectively harness endogenous or induced plasticity in specific motor pools as a treatment for diverse ventilatory control disorders.

2. Does LTF reflect mechanisms operating within motor neurons?

Since this special issue is focused on respiratory motor neurons, we will briefly comment on evidence that the mechanisms responsible for pLTF and hLTF occur (at least in part) *within* phrenic and hypoglossal motor neurons, respectively. Although LTF of nerve burst amplitude is frequently hypothesized to reflect mechanisms operating within respiratory motor neurons (Baker-Herman et al., 2010; Feldman et al., 2003; Ling, 2008; Mahamed and Mitchell, 2007; Mitchell et al., 2001), there is no definitive evidence to date that supports or refutes this hypothesis. Local (spinal) mechanisms are certainly important for pLTF since inhibition of key molecules in regions of the cervical spinal cord associated with the phrenic motor nucleus selectively block pLTF, but not hLTF (Baker-Herman and Mitchell, 2002; MacFarlane et al., 2009; McGuire et al., 2005; Mahamed and Mitchell, 2008). Although a similar dissociation of pLTF and hLTF by local, targeted inhibition of key cellular pathways in or near the hypoglossal motor nucleus has not yet been demonstrated, local mechanisms are also likely required for hLTF. Indeed, local mechanisms operating at the level of the hypoglossal motor nucleus are required for hypoglossal motor facilitation (hMF) induced by vagal feedback (Tadjalli et al., 2010).

While available data suggest that mechanisms in or near the respiratory motor pool are key for LTF, the cell types (i.e., glia, interneurons, motor neurons, presynaptic terminals of brainstem neurons providing respiratory drive, etc.) in which these mechanisms are occurring is unknown. Mechanisms operating within motor neurons are sufficient to induce prolonged increases in respiratory-related burst amplitude (discussed below; Bocchiaro and Feldman, 2004; Neverova et al., 2007), at least for neonatal hypoglossal motor neurons. However, it is not yet known whether these same mechanisms are relevant in adult rats or following AIH.

3. What similarities exist between pLTF and hLTF?

To our knowledge, only three features of LTF are currently known to be similar in the phrenic and hypoglossal motor pools: pattern sensitivity (J.E.R. Wilkerson and G.S. Mitchell, personal