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Chronic intermittent hypoxia creates the perfect storm with calamitous consequences for respiratory control.

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ABSTRACT

Obstructive sleep apnoea syndrome (OSAS) is a common respiratory disorder with devastating consequences for integrative body systems. A picture is emerging to illustrate wide-ranging deleterious consequences of disordered breathing during sleep for major homeostatic control systems, with considerable interest in cardiorespiratory and autonomic morbidity underpinning the development of hypertension. The vista is bleak when one also considers the link between OSAS and a host of other maladies. Exposure to chronic intermittent hypoxia (CIH), resulting from repeated obstructions of the pharyngeal airway, is a hallmark feature of OSAS that appears, in animal models, to drive the development and maintenance of several key morbidities. A growing body of evidence now points to aberrant respiratory plasticity at multiple levels following exposure to CIH. Herein, we review the experimental data revealing that CIH causes: respiratory muscle weakness and fatigue; impaired motor control of the upper airway; and, discordant respiratory rhythm and pattern generation. This multifaceted conspiracy creates the perfect storm with the potential to exacerbate OSAS—serving to establish an inescapable cycle of respiratory morbidity. Several pharmacological interventions in animal models appear wholly effective in preventing the calamitous consequences of CIH and may have application as adjunctive therapies in the treatment of OSAS.

1. Overview

What cares these roarers
for the name of king?
Shakespeare - *The Tempest*

Disordered breathing during sleep is common and has potentially devastating consequences for normal body function. Obstructive sleep apnoea syndrome (OSAS), the most common form of sleep-disordered breathing (SDB), has scant regard it seems for homeostatic control systems of major body functions, with long-standing evidence of strong associations between OSAS and cardiovascular, metabolic and neurocognitive morbidities. Emerging evidence disturbingly points to a flood of new maladies, suggesting that there is no safe harbour for any organ system in OSAS, firmly framing the syndrome as a major public health issue. SDB is characterized by repeated waves of hypoxia and re-oxygenation due to recurrent apnoea (cessation of airflow) during sleep. There is evidence from studies in animals and humans to suggest that intermittent hypoxia (IH) overwhelms the respiratory control system at multiple levels. In this short review, we examine the evidence, in animal models, that exposure to chronic IH (CIH) has adverse effects on respiratory muscle form and function, motor control of upper airway calibre, and coordinated respiratory rhythm and pattern generation, conspiring to create the perfect storm with calamitous consequences for the control of breathing.

Herein we consider the evidence that exposure to CIH causes respiratory muscle weakness and/or fatigue. Altered redox status and mitochondrial dysfunction likely underpins aberrant muscle plasticity following exposure to CIH. Neural control of the respiratory muscles, particularly motor control of the upper airway is also adversely affected by CIH, due to oxidative damage of brainstem motor nuclei. It is also apparent that impaired control of upper airway dilator muscles translates to increased collapsibility of the upper airway following exposure to CIH. Moreover, CIH alters peripheral and central network control of breathing with altered expression of the respiratory motor 'signature', with resultant unstable breathing and an increased propensity for central apnoea. Thus, it appears that CIH orchestrates an inescapable cycle that could serve to perpetuate respiratory disorders such as human OSAS.

Some encouraging findings in animal models suggest that hope, in the form of interventional therapeutic strategies, may be on the horizon. Consistent with observations in other body systems,

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CIH drives a pro-oxidant state that drowns antioxidant defences, with recent evidence pointing to enhanced superoxide production from cytosolic oxidases. Antioxidant and other emerging treatments are effective in blocking or ameliorating the deleterious effects of CIH on the respiratory control system and therefore might prove effective as adjunctive treatments in OSAS and other respiratory conditions characterized by CIH. Of considerable interest, oestrogen appears to protect respiratory muscles from the injurious effects of CIH and phytoestrogens have been shown to be effective experimentally.

2. Sleep-disordered breathing

The human pharynx lacks bony and cartilaginous support and consequently is quite vulnerable to collapse (Schwab, 1998), especially during inspiration when a sub-atmospheric ('negative') pressure is generated in the upper airway due to activation of the inspiratory pump muscles, principally the diaphragm (Remmers et al., 1978; White and Younes, 2012). Over 20 muscles participate in the co-ordinated regulation of upper airway patency. Reflex activation of the pharyngeal dilator muscles protects airway patency on a breath-by-breath basis and is critically important in recovering airflow following collapse of the highly compliant pharyngeal segment (Remmers et al., 1978; Jordan et al., 2007; White and Younes, 2012). Repetitive collapse of the upper airway exclusively during sleep, associated with arterial oxygen desaturations, is a hallmark feature of OSAS (White and Younes, 2012). Occlusion of the pharynx occurs when the dilative forces produced by the upper airway muscles are insufficient to counterbalance the collapsing force produced by the inspiratory pump muscles (Remmers et al., 1978; Schwartz et al., 1998). Arousals from sleep are typically required to restore airway patency and re-establish pulmonary ventilation, resulting in daytime hypersomnolence (Jordan et al., 2011). Multiple factors contribute to the pathogenesis of OSAS but sleep-related decrement in upper airway dilator muscle tone in individuals with congenital or acquired abnormal airway anatomy is a key component of the disorder.

Several research groups have focussed attention on the contractile and endurance properties of the upper airway muscles, since the mechanical performance of these muscles is an important determinant of pharyngeal stability. Upper airway muscle dysfunction is implicated in the pathophysiology of OSAS (Series et al., 1995; Carrera et al., 1999; Kimoff, 2007). The pump and airway dilator respiratory muscles retain considerable capacity for structural and functional plasticity in response to changes in functional demands. Under pathophysiological conditions such as OSAS, the upper airway dilator muscles have increased functional demands that can result in 'maladaptive' changes that serve to further compromise upper airway stability. It is speculated that impaired function of the upper airway muscles increases the susceptibility to collapse and may trigger a vicious cycle perpetuating obstructive airway conditions (Petrof et al., 1996; Bradford et al., 2005; Kimoff, 2007).

3. Chronic intermittent hypoxia impairs upper airway muscle function

Bradford and colleagues (McGuire et al., 2002a, 2002b; Bradford et al., 2005) were the first to show that CIH — modelling severe sleep apnoea — alters respiratory muscle function. Since those early studies, several independent studies have reported upper airway muscle weakness and/or fatigue following exposure to CIH (McGuire et al., 2002a,b; Liu et al., 2005, 2009 Pae et al., 2005; Dunleavy et al., 2008; Jia and Liu, 2010; Ding and Liu, 2011; Skelly et al., 2012; Wang et al., 2013; Zhou and Liu, 2013; McDonald et al., 2015), notwithstanding notable differences in the pattern and duration of CIH exposures employed in the different studies. CIH-induced upper airway muscle dysfunction does not require structural remodelling in the form of atrophy and/or fibre type transitions (Skelly et al., 2012a,b; McDonald et al., 2015), though fibre-type transitions have been described (McGuire et al., 2002a; Liu et al., 2009), including increases in the proportion of fast myosin heavy chain 2B fibres (Pae et al., 2005), consistent with observations of increased airway dilator muscle fatigue. Of note, slow-to-fast fibre transitions are observed in human OSAS (Smirne et al., 1991; Series et al., 1995, 1996, 1999; Carrera et al., 1999, 2004), and the relative area of fast fibres is increased in the English bulldog model of OSAS (Petrof et al., 1994). Upper airway muscle dysfunction following exposure to CIH is dependent on the duration IH exposure (Pae et al., 2005). There is some evidence to suggest that the effects may also be age- and sex-dependent. Skelly et al. (2012a) reported sternohyoid muscle weakness in male, but not female rats, following CIH. A follow-up study (Skelly et al., 2012b), employing the same CIH paradigm, revealed decreased susceptibility to CIH-induced muscle dysfunction in middle-aged male rats, consistent with the findings of others who reported a lack of structural and functional change in the upper airway muscles of aged Zucker rats (Ray et al., 2007). In comparison, a recent study reported sternohyoid muscle weakness following neonatal exposure to CIH (McDonald et al., 2015), with increased susceptibility to CIH compared with adult animals (McDonald et al., 2014, 2015). Moreover, sternohyoid muscle dysfunction following early-life exposure to CIH extends into young adulthood suggesting long-lasting airway dilator muscle impairment following exposure during critical windows of development (McDonald et al., 2015). CIH has also been shown to increase genioglossus muscle (principal airway dilator) fatigue (Liu et al., 2009; Jia and Liu, 2010; Ding and Liu, 2011; Zhou and Liu, 2013; Wang et al., 2013; Huang et al., 2014), most likely in a HIF-1α-dependent manner (Jia amd Liu, 2010) associated with mitochondrial dysfunction (Huang et al., 2014). Genioglossus dysfunction presents in ovariectomized female rats and it is prevented by oestrogen replacement therapy (Liu et al., 2009; Jia and Liu, 2010; Huang and Liu, 2011; Zhou and Liu, 2013).

CIH-induced muscle plasticity is not restricted to the muscles of the upper airway; indeed a widespread effect on skeletal muscle has been reported (McGuire et al., 2003a). Although short-term IH exposure (hours) was shown to have no effect on diaphragm structure and contractile function (Pae et al., 2005), Clanton et al. (2001) reported increased force generation and improved anoxic tolerance in isolated diaphragm following 10 days of IH, with no effect on muscle fatigue. Subsequently, Shortt et al. (2014) demonstrated that diaphragm force and fatigue were affected in a manner dependent on the duration and intensity of the CIH exposure, with weakness and fatigue reported following a 2 week exposure to IH. Structural analysis revealed no evidence for muscle atrophy but an increase in the relative area of myosin type 2B fibres (Shortt et al., 2013, 2014), consistent with observations in airway dilator muscles (Pae et al., 2005), and with observations of CIH-induced decreased respiratory muscle endurance (Pae et al., 2005; Shortt et al., 2014). Increased diaphragm fatigue was also observed following 5 weeks of CIH exposure (McGuire et al., 2003a). Interestingly, it has also been demonstrated that CIH can exacerbate diaphragm muscle weakness in *mdx* dystrophic mice (Farkas et al., 2007). Beyond the respiratory muscles, McGuire et al. (2003a) also reported decreased endurance and recovery from fatigue in slow- and fast-twitch limb muscles after 5 weeks of IH exposure. This generalized effect of CIH on skeletal muscle suggests a direct deleterious effect of the hypoxia/re-oxygenation cycles on muscle function *per se* and potentially extends the ramifications of muscle dysfunction following CIH in human OSAS to whole-body effects.