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Breathing with neuromuscular disease: Does compensatory plasticity in the motor drive to breathe offer a potential therapeutic target in muscular dystrophy?

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ABSTRACT

Duchenne muscular dystrophy is a fatal neuromuscular disease associated with respiratory-related morbidity and mortality. Herein, we review recent work by our group exploring deficits and compensation in the respiratory control network governing respiratory homeostasis in a pre-clinical model of DMD, the *mdx* mouse. Deficits at multiple sites of the network provide considerable challenges to respiratory control. However, our work has also revealed evidence of compensatory neuroplasticity in the motor drive to breathe enhancing diaphragm muscle activity during increased chemical drive. The finding may explain the preserved capacity for *mdx* mice to increase ventilation in response to chemoactivation. Given the profound dysfunction in the primary pump muscle of breathing, we argue that activation of accessory muscles of breathing may be especially important in *mdx* (and perhaps DMD). Notwithstanding the limitations resulting from respiratory muscle dysfunction, it may be possible to further leverage intrinsic physiological mechanisms serving to compensate for weak muscles in attempts to preserve or restore ventilatory capacity. We discuss current knowledge gaps and the need to better appreciate fundamental aspects of respiratory control in pre-clinical models so as to better inform intervention strategies in human DMD.

1. Duchenne muscular dystrophy (DMD): respiratory morbidity and mortality

Dystrophin is a structural protein that prevents stretch-induced muscle damage during contraction by anchoring the actin cytoskeleton to the sarcolemma (Petrof et al., 1993). In the absence of dystrophin, muscle damage occurs resulting in muscle fibre necrosis and extensive muscle weakness. Skeletal muscle function is adversely affected in the dystrophinopathies, with attendant muscle fibrosis and secondary inflammation. The striated muscles of breathing are implicated in the disease with evidence of diaphragm muscle weakness (Khirani et al., 2014), which has major implications for the control of breathing in DMD.

Respiratory morbidity and mortality are common features of many neuromuscular diseases (Bye et al., 1990). Many boys with DMD experience respiratory disturbances during life, while cardio-respiratory failure remains the leading cause of death. Pulmonary function peaks when patients are in their mid-teens, although forced vital capacity (FVC) values remain lower than predicted (De Bruin et al., 2001; Phillips et al., 2001; Khirani et al., 2014). Thereafter, there is a steady decrease in FVC with increasing age at a rate of approximately 5% of predicted values per year (Baydur et al., 1990; Phillips et al., 2001; Roberto et al., 2011; Khirani et al., 2014; Mayer et al., 2015; Meier et al., 2017). Trans-diaphragmatic pressure during sniff behaviours are reported to be low in DMD compared with predicted values of normal subjects (Khirani et al., 2014). Trans-diaphragmatic pressure declined steadily in DMD boys after 10 years of age at an average rate of ~4 cm H_2O per year (Khirani et al., 2014), revealing a progressive impairment of diaphragm mechanical function. An examination of gastric pressure during cough in DMD boys revealed gastric pressures to be low (compared with predicted values) declining at a rate of ~6 cm H_2O per year (Khirani et al., 2014). Collectively, these data indicate compromised inspiratory and expiratory muscle strength as a result of dystrophin deficiency in DMD, with implications for the control of breathing.

Patients with DMD experience disruptions to breathing, particularly during sleep (Arens and Muzumdar, 2010). Patients are known to suffer from sleep apnoea with both obstructive and central apnoeas described, with subsequent disruptions to arterial blood oxygenation levels (Barbé et al., 1994; Khan and Heckmatt, 1994). Evidence suggests that patients have a greater risk of oxygen desaturation during sleep with increasing

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age (Khan and Heckmatt, 1994), which is most likely due to obstructive apnoea during the first decade of life (Suresh et al., 2005). Studies reporting the apnoea-hypopnea index in DMD suggest that patients suffer from moderate sleep apnoea (Smith et al., 1989a; Bersanini et al., 2012). As patients reach the second decade of life, they are at an increased risk of hypoventilation during sleep (Smith et al., 1989b; Suresh et al., 2005), culminating in hypoxaemia during sleep (Smith et al., 1988; Barbé et al., 1994; Khan and Heckmatt, 1994) and nocturnal hypercapnia (Baydur et al., 1990; Mohr and Hill, 1990; Bersanini et al., 2012). Patients are known to develop scoliosis, further impacting on respiratory function. There are significant gaps in the understanding of neuromechanical factors controlling breathing and non-ventilatory behaviours such as airway clearance manoeuvres and swallowing in patients with neuromuscular disease. Studies examining the prevalence of respiratory impairment in neuromuscular diseases such as DMD are lacking.

2. The dystrophin-deficient *mdx* mouse: diaphragm dysfunction recapitulating human DMD

The *mdx* mouse is a mutant model of DMD. Dystrophic diaphragm muscle from *mdx* mice exhibits severe mechanical dysfunction and muscle weakness as early as 6 weeks of age (Coirault et al., 2003) and persists throughout life (Stedman et al., 1991; Stevens and Faulkner, 2000; Whitehead et al., 2016). Deficits include reduced force- and power-generating capacity and reduced muscle elasticity and fibre length (Stedman et al., 1991; Coirault et al., 1999; Burns et al., 2017a). Moreover, *mdx* diaphragm shows evidence of inflammation, centralised myonuclei and fibrosis (Stedman et al., 1991; Coirault et al., 2003; Huang et al., 2009). Structural alterations in myosin heavy chain (MyHC) isoform composition are observed, with dystrophic diaphragm expressing a reduced number of MyHC IIx fibres and increased MyHC IIa fibres (Coirault et al., 1999) compared with wild-type due to ongoing damage and repair processes. Few studies have examined the functional consequences of dystrophin deficiency on ventilatory capacity in *mdx* mice. Impaired normoxic ventilation was reported in 2 month old and 6 month old *mdx* mice (Mosqueira et al., 2013; Burns et al., 2015). In addition to diaphragm muscle weakness, the musculature of the upper airway is also compromised by dystrophin deficiency in the *mdx* mouse (Attal et al., 2000; Burns and O'Halloran, 2016). Muscle weakness, inflammation, fibrosis and central nucleation are described in the dystrophic sternohyoid muscle, a representative pharyngeal dilator (Burns et al., 2017b). Considerable deficits in sternohyoid muscle force- and power-generating capacity are present in *mdx* mice at 8 weeks of age (Burns and O'Halloran, 2016; Burns et al., 2017b) and 6 months of age (Attal et al., 2000). Similar to the diaphragm, structural alterations in MyHC isoform composition are evident in *mdx* sternohyoid muscle, with dystrophic sternohyoid expressing a decreased number of MyHC IIb and an increased number of MyHC IIx fibres (Attal et al., 2000; Burns et al., 2017b).

3. Control of breathing in the *mdx* mouse: neural adaptation or maladaptation?

There is now a large body of evidence revealing a remarkable capacity for plasticity at multiple sites within the respiratory control network governing control of arterial blood gases and pH (Huey et al., 2003; Mitchell and Johnson, 2003; Bavis et al., 2007; Kumar and Prabhakar, 2012; Fuller and Mitchell, 2017). Sensory and motor plasticity is context-dependent and can elaborate overt adaptive or maladaptive outcomes (Baker et al., 2001; Peng et al., 2003; Prabhakar, 2011; Wilkerson et al., 2017). Compensatory neuroplasticity at one or more sites of the integrative network could ameliorate respiratory system compromise in DMD. Conversely, deficits in the sensory (afferent) or motor (efferent) control of breathing could further compound respiratory morbidity, disrupting respiratory homeostasis potentially establishing a spiral of disability. Until recently, the impact of dystrophin deficiency on the neural control of breathing was unclear. We performed the first broad assessment of sensory and motor control of breathing in *mdx* mice (Burns et al., 2017c). We reasoned that there would be evidence of neuroplasticity of relevance to respiratory homeostasis at one or more sites of the respiratory control network of the *mdx* mouse.

4. Control of breathing in the *mdx* mouse: deficits and dysfunction

We studied young adult male *mdx* mice given our interest in the early impact of dystrophin deficiency on the control of breathing. In *mdx* mice at 8 weeks of age, we confirmed the appearance of profound diaphragm muscle weakness. Isometric force-generating capacity of *ex vivo* diaphragm preparations was depressed by ~40% compared with age-matched wild-type control diaphragms (Burns et al., 2017c). Immunohistochemistry performed on diaphragm muscle cross-sections revealed a greater abundance of small diameter fibres and increased coefficient of variation of muscle fibre size, which together with an increased density of centrally-nucleated fibres (indicative of myonecrosis) demonstrated considerable muscle remodelling in the *mdx* diaphragm (Burns et al., 2017c). Notwithstanding that intrinsic weakness in *mdx* diaphragm is substantial at a young age, the large reserve capacity of the diaphragm is such that diaphragm dysfunction would not ordinarily be expected to place considerable limits on ventilatory performance, but would affect important non-ventilatory behaviours such as airway clearance manoeuvres (Mantilla et al., 2010; Mantilla and Sieck, 2011).

However, hypoventilation during baseline normoxic breathing was evident at 8 weeks of age in *mdx* compared with wild-type mice (Burns et al., 2017c). There was a significant decrease in the ventilatory equivalent for carbon dioxide (V_E/VCO_2) in *mdx* mice, the principal deficit arising from a significant reduction in baseline tidal volume. Intra-cardiac blood gas analysis in isoflurane anaesthetized *mdx* mice demonstrated the development of a compensated respiratory acidosis.

Dystrophin is expressed in the carotid body (Mosqueira et al., 2013). We explored carotid body afferent discharge frequency and responsiveness to hypoxia in isolated perfused carotid body-carotid sinus nerve preparations to determine if sensory deficit presents and contributes to ventilatory impairment in *mdx* mice (Burns et al., 2017c). A relative hypoactivity of the carotid body was revealed during normoxia, with evidence of a blunted inhibitory response to hyperoxia in *mdx* preparations compared with wild-type preparations. However, the classic excitatory chemosensory response to hypoxia was not significantly different between *mdx* and wild-type carotid bodies. The latter finding was consistent with observations of equivalent hypoxic ventilatory responses in *mdx* and wild-type mice (Burns et al., 2017c). Since sensory inputs from the peripheral chemoreceptors provide tonic drive to eupnoeic breathing, carotid body hypoactivity might contribute, at least in part, to resting hypoventilation in *mdx*. Some additional potential factors contributing to resting hypoventilation in *mdx* mice are discussed below.

5. Control of breathing in the *mdx* mouse: compensation and limitations

In our recent study (Burns et al., 2017c), we recorded diaphragm EMG activity during baseline and in response to chemoactivation of breathing during hypercapnic hypoxic (asphyxic) challenge. Baseline EMG activity was equivalent between wild-type and *mdx* mice, but the magnitude of the increased EMG activity in response to asphyxia was significantly enhanced in *mdx* mice. The response is suggestive of compensatory neuroplasticity in the motor control of breathing. Since chemosensory responses were equivalent between wild-type and *mdx* mice, we concluded that increased neural drive was reflective of an increased gain in the control system at the level of key integrative sites

in the brainstem network and/or at the level of the spinal phrenic motor pool innervating the diaphragm. It will be important to establish if increased efferent drive is revealed in phrenic neurogram recordings. We are currently exploring this issue with evidence of potentiated phrenic nerve activity in *mdx* mice in response to maximum chemostimulation (Burns et al., unpublished observations).

Whereas diaphragm EMG responsiveness was significantly increased in *mdx*, the profound weakness of the major muscle of breathing is such that transduction of enhanced neural drive to the mechanical act of breathing is likely compromised during behaviours associated with high demand. Of note, *mdx* mice are capable of increasing ventilation in response to increased chemical drive to breathe. In our study, the ventilatory response to hypercapnia was equivalent in wild-type and *mdx* mice (Burns et al., 2017c). It is established that motor recruitment of the diaphragm in response to hypercapnia is submaximal, operating below 30% of the maximum capacity of the system (Mantilla et al., 2010; Greising et al., 2013). As such, increased neural drive and a right-ward shift of the force-frequency relationship in *mdx* diaphragm might provide increased and sufficient diaphragm force-generating capacity, notwithstanding the significant deficit in *mdx* muscle compared with wild-type (Fig. 2). However, it is important to recognise that increased neural drive to the diaphragm and recruitment of the largest motor units appears to have a limited capacity to achieve non-ventilatory behaviours due to significant muscle weakness even during peak activation. It is also conceivable that increased drive in motor pathways to accessory muscles of breathing facilitates tidal breathing in *mdx* mice. If neuroplasticity extends to multiple parallel efferent pathways, arising for example from enhanced central respiratory drive to breathe during chemoactivation, recruitment of accessory inspiratory muscles of breathing might help to preserve ventilatory capacity in response to chemoactivation (Johnson and Mitchell, 2013). Indeed, activation of accessory muscles of breathing may be important in *mdx* (and perhaps DMD) across the spectrum of ventilatory and especially non-ventilatory behaviours. Interestingly, there is evidence of expiratory muscle recruitment to facilitate ventilation in the Golden Retriever model of muscular dystrophy (Mead et al., 2014). It is established that active expiration facilitates tidal volume generation by altering the length-tension relationship of the diaphragm, and increasing intra-abdominal pressure lowering end-expiratory lung volume, which increases inspiratory capacity (Sherrey et al., 1988; Road et al., 1991; Sieck et al., 2013). Active expiration may support ventilatory capacity in *mdx* and DMD, at least under some circumstances. If compensatory neuroplasticity presents in efferent motor pathways in DMD, it may be possible to further boost neural drive to breathe and in this way help preserve ventilatory capacity. A major drawback with such an approach are the limits afforded by the final effector organs, the respiratory muscles, and potential concerns associated with activity-induced damage, since it is known that exercise in *mdx* mice exacerbates muscle dysfunction, including diaphragm dysfunction (Selsby et al., 2013). Whereas, diaphragm dysfunction is recognised in dystrophin-deficient animal models and human DMD, there is a current paucity of knowledge in respect of accessory muscle form and function, which represents a crucial gap in the current knowledge base. Harnessing putative plasticity in accessory motor pathways may offer an attractive therapeutic strategy in DMD.

Despite evidence in support of neuroplasticity in the major neural efferent pathway supporting breathing (Burns et al., 2017c), we observed that *mdx* mice hypoventilated at rest, even though animals were capable of increasing ventilation in response to hypoxia and hypercapnia. One possibility is that mice were sleeping during basal measurements. Indeed, our assessment of behaviour and respiratory indices (e.g. respiratory frequency ~180 breaths/min) is consistent with this suggestion. There may have been exaggerated sleep-related hypoventilation in *mdx* compared with wild-type mice. Of note, diaphragm muscle activity is well preserved during sleep (Parmeggiani, 1978; Duron and Marlot, 1980; Orem and Anderson, 1996), but accessory muscle activity is state-dependent (Duron and Marlot, 1980; Megirian et al., 1987; Pagliardini et al., 2013). Sleep-related reductions in accessory muscle support of breathing in *mdx* may have contributed to hypoventilation (Burns et al., 2017c), which interestingly is also observed in sleeping DMD patients. A similar phenomenon of state-dependent neuromuscular compensation is described in people with obstructive sleep apnoea (Mezzanotte et al., 1992, 1996), wherein enhanced upper airway muscle activity preserves pharyngeal calibre during wakefulness, but sleep-related hypotonia in upper airway muscles due to reductions in cranial motor drive occurring naturally in sleep results in loss of neuromuscular compensation of airway patency resulting in airway collapse in individuals with vulnerable airways. Whereas subsequent work questioned the validity of neuromuscular compensation in obstructive sleep apnoea drawing focus to upper airway muscle injury and dysfunction (Kim et al., 2014; O'Halloran, 2014), relevant to DMD, a similar phenomenon of state-dependent accessory neuromuscular compensation may apply to *mdx* mice and DMD patients. Of note, sleep enhances active expiration in rats (Leirão et al., 2017; O'Halloran, 2017), which argues against a potential role for active expiration in the control of basal breathing in *mdx* mice. Sleep also affects posture, which is known to influence accessory muscle activity (Duron and Marlot, 1980; Megirian et al., 1987; Hudson et al., 2010, 2011). As such, postural changes in mice and perhaps humans during rest/sleep may influence neuromechanical control of tidal breathing reducing putative accessory muscle support of ventilation. Scoliosis in human DMD is also likely to affect accessory muscle performance, which may have implications for control of breathing across a range of behaviours. However, if one reasons that sleep did not likely affect motor drive to the diaphragm (Duron and Marlot, 1980), and acknowledges the large ventilatory reserve in the diaphragm (Mantilla et al., 2010) notwithstanding the considerable deficits in *mdx*, it is difficult to conclude that hypoventilation arises owing to mechanical disadvantage. Perhaps sensory deficit (carotid body hypoventilation) is sufficient to cause resting hypoventilation in *mdx* mice, which could be further exaggerated during sleep.

6. Control of breathing in the *mdx* mouse: knowledge gaps

There is a surprising dearth of information in respect of the neural control of breathing in the dystrophinopathies, notwithstanding that respiratory morbidity and mortality are dominant features. More studies are required to understand the extent of respiratory system deficit and compensation, and the temporal changes over the course of disease progression. Knowledge of fundamental aspects of respiratory control is essential in the consideration of respiratory management of patients with neuromuscular disease. Moreover, a better appreciation of the intrinsic compensatory processes at play in DMD should help inform therapeutic strategies. Our study revealed enhanced diaphragm EMG responsiveness in *mdx* mice suggestive of compensatory neuroplasticity. However, in a myopathy model such as *mdx*, EMG recordings may be contaminated by aberrant motor unit potentials associated with dynamic degeneration and regeneration of muscle fibres. On-going studies by our group of phrenic neurogram responses to chemoactivation in *mdx* mice are addressing this point. It is unclear whether motor activation of accessory muscles is altered in *mdx* and this represents an important gap in the understanding of respiratory control in dystrophin-deficient neuromuscular disease. Moreover, the extent of accessory muscle dysfunction compared with diaphragm, and whether neuromechanical coupling in accessory muscles is effective in supporting ventilatory capacity in *mdx* (and DMD) remain to be determined. Assessment of the control of breathing including respiratory electromyogram activity across the sleep-wake cycle during progressive disease is required. Studies are required to address these issues and determine if therapeutic strategies exploiting accessory pathways represents a viable interventional option aimed at increasing ventilatory capacity, with a view to treatment options for DMD patients. A

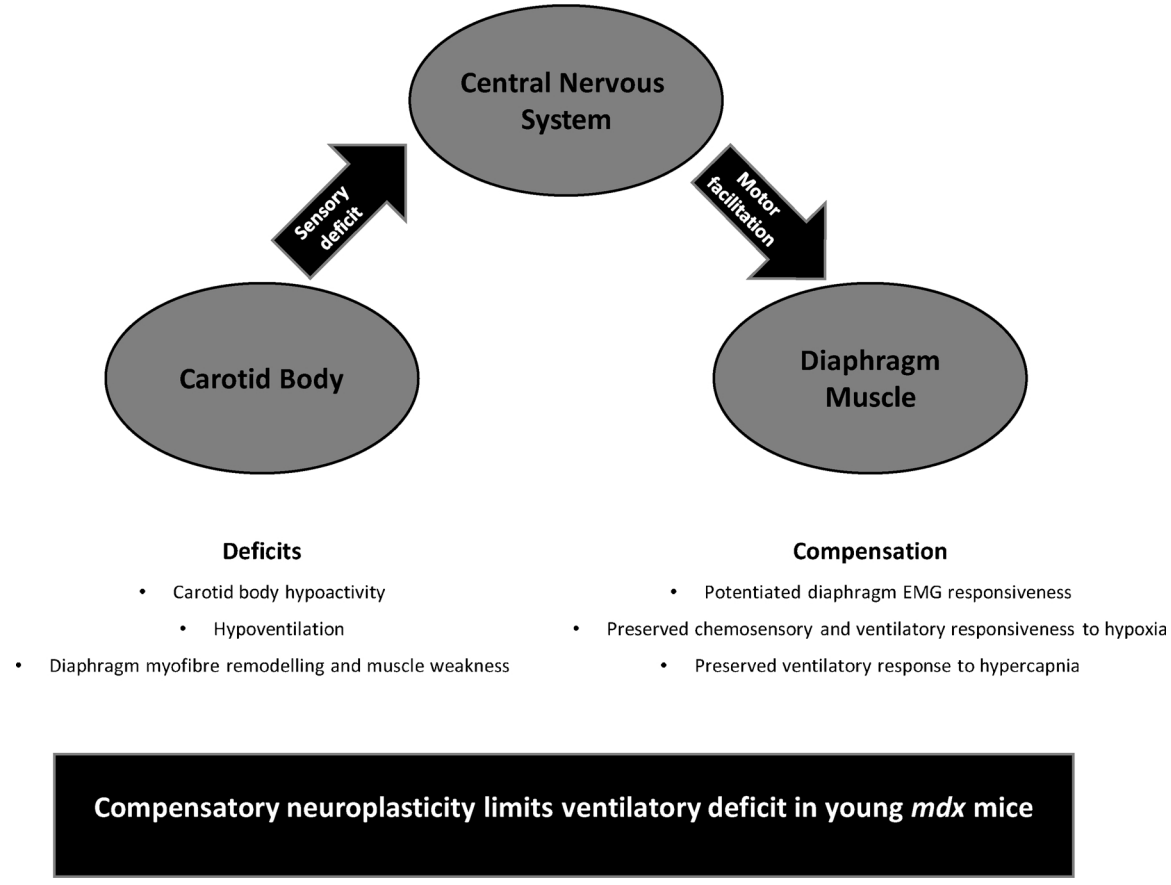

Fig. 1. Summary of the deficits and compensation in respiratory control in young adult *mdx* mice. Adapted from data presented in Burns et al. (2017c).

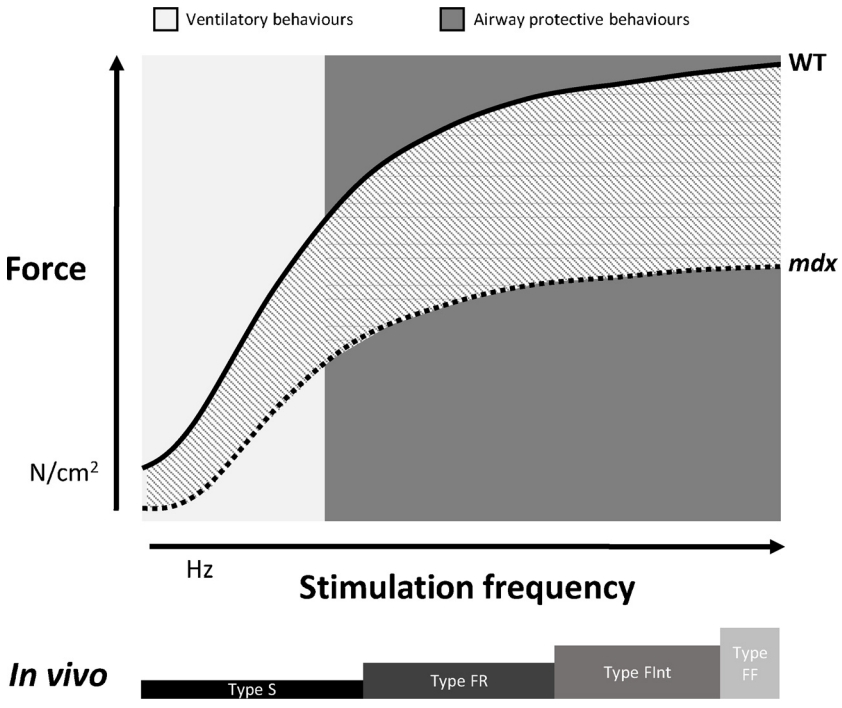

Fig. 2. Schematic representation of diaphragm force-frequency relationship in wild-type (WT) and dystrophin-deficient *mdx* mice determined in *ex vivo* preparations. Deficits in force-generating capacity are seen in the range relevant to ventilation and airway protective behaviours. Enhanced neural drive during chemoactivation has limited capacity to increase diaphragm force, compared with wild-type, suggesting that preserved ventilatory capacity in *mdx* during chemostimulation may be especially dependent on accessory muscles of breathing. Adapted from data presented in Burns et al. (2017c). The bottom schematic, informed by the studies of Sieck and Mantilla (Mantilla et al., 2010, 2014), illustrates the major motor unit types associated with graded force-generating capacity of the *in vivo* diaphragm.

summary of the effects of dystrophin-deficiency on respiratory control in young adult *mdx* mice is shown in Fig. 1.

7. Control of breathing in the *mdx* mouse: therapeutic intermittent hypoxia to boost respiratory drive?

In recent years, Mitchell et al. have pioneered the understanding and potential exploitation of mechanisms of motor plasticity to enhance

respiratory motor output (Fuller and Mitchell, 2017). Manipulating environmental oxygen in the form of acute bouts of intermittent hypoxia has the capacity to evoke ventilatory long-term facilitation (LTF) in behaving rodents (Edge and O'Halloran, 2015). Furthermore, intermittent hypoxia-induced LTF is well described in motor pathways of the diaphragm (Fuller et al., 2000), upper airway (Wilkerson et al., 2017) and accessory muscles of breathing such as the intercostal muscles (Navarrete-Opazo and Mitchell, 2014). We reason that safe interventions aimed at evoking plasticity in the motor pathways of breathing may have therapeutic capacity to facilitate breathing in *mdx* mice, as has been elegantly demonstrated in rodent models of motor neuron loss (Nichols et al., 2013, 2015) and spinal cord injury (Dougherty et al., 2017). This warrants attention in future studies, but may face challenge in the context of systemic inflammation, a feature of dystrophin deficiency, which suppresses motor facilitation of breathing (Huxtable et al., 2011).

8. Conclusion

Dystrophin-deficiency has detrimental consequences for respiratory control. We have revealed a broader vista of the deficits that present early in a pre-clinical model of neuromuscular disease, the *mdx* mouse. We also have revealed, for the first time, compensatory adjustments in the nervous system control of respiratory muscles in *mdx* mice striving for homeostatic control of breathing. We suggest that it may be possible to exploit intrinsic physiological mechanisms serving to boost breathing in the development of therapeutic strategies for DMD, through the use of safe interventional therapies such as intermittent hypoxia.

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