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PERSPECTIVE

Oxygen deprivation is a muscle revelation: hypoxia enhances motor unit firing after spinal cord injury

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Spinal cord injury (SCI) can have devastating and life-long consequences that are dependent on the location and magnitude of trauma to the cord. Although it is difficult to account for every worldwide incident, the World Health Organization estimates that over 15 million people globally live with a condition that is categorised as SCI. In the absence of a cure, there is an urgent need to develop cost-effective, time-efficient, and above all, evidence-based therapies that can be implemented in a clinical setting. One promising approach is to induce motor recovery via spared neural pathways in the damaged cord by exploiting mechanisms of endogenous neuroplasticity. Specifically, routine exposure to intermittent hypoxia may induce long-term adaptations in spinal circuits by promoting monoaminergic activity in the motor system.

An initial step to understanding why repeated hypoxic exposure may cause neuroplasticity in SCI motor circuits is to assess the short-term consequences of the intervention. In this issue of *The Journal of Physiology*, Pearcey et al. (2024) examine how a single bout of acute intermittent hypoxia (AIH) affects motor unit discharge in a cohort of patients with incomplete SCI between C4 and C7. All patients had a Spinal Injury Association Impairment Scale of C or D, indicating that the function of some motor pathways was preserved below the neurological level. Thus, using high-density electromyography (HD-EMG) to examine muscles of the upper limb could provide insight to torque generation and motor unit behaviour following SCI. This work complements a previous study (Afsharipour et al., 2023) to provide evidence that AIH has a facilitatory effect on motor unit discharge rate in biceps and triceps brachii during maximal effort contractions. Importantly, this change in muscle activation transfers to an increased capacity to generate flexion and extension torque about the elbow joint – a key metric in quantifying functional recovery during rehabilitation. Perhaps the most impressive finding of this study was that maximal flexion torque increased by 54% and maximal extension torque increased by 59% following just 15 exposures to 9% O_2 for 1 min each (alternated with 1 min exposures to normoxic 21% O_2). This rapid motor response to a single bout of AIH will no doubt spawn future work to optimise this therapy that could be performed over a period of weeks, months or years.

The authors propose that AIH-related increases in motor unit firing could arise from direct and indirect serotonergic influences on motoneurone excitability. This viewpoint has merit as monoamines are present below the level of injury in incomplete SCI, and AIH-induced 5-HT release into the spinal cord could act on the remaining intact motor pathways. However, the exact mechanism of 5-HT action in humans remains elusive and forms an exciting prospect for future AIH research. For instance, if 5-HT concentration in the spinal cord is increased with AIH, the increased 5-HT would need to be effective at the motoneurone. Receptor subtypes, distributions and binding affinities all guide the ability to harness additional 5-HT in the CNS, so understanding the effects of AIH on these mechanisms will be crucial to understand how motor unit behaviour changes with AIH (Tadjalli & Mitchell, 2019). Understanding AIH mechanisms in SCI is even more complex when considering the role of neurotrophic factors. Neurotrophic factors like brain-derived neurotrophic factor (BDNF) are not just influenced by AIH but can also promote receptor gene expression following trauma to the spinal cord. It is known that following SCI there is constitutive receptor activation of 5-HT and α-receptors on motoneurones (D'Amico et al., 2014). Importantly, the receptor subtypes that are expressed on spinal motoneurones are mediators of motor unit firing rates in humans (e.g. 5-HT$_2$ and α1). Thus, 5-HT and noradrenaline release from brainstem pathways, as well as changes in gene expression and receptor activation on motoneurones, may interact in a complex manner during the administration of AIH to incomplete SCI patients.

Investigations that enhance motor function have typically induced AIH by regulating $F_{\mathrm{iO_2}}$ or $S_{\mathrm{pO_2}}$ levels. However, there may be considerable scope in future work to control arterial $P_{\mathrm{CO_2}}$ to manipulate hypercapnia in SCI patients. CO_2 is known to directly activate the 5-HT-producing raphe nucleus in the brainstem, and a combined hypoxia and hypercapnia approach may synergistically enhance raphe nuclei activity and downstream signalling in target motoneurones (refer to Vose et al., 2022). However, it is important to note that most SCI experiments that provide evidence for 5-HT or AIH mechanisms have examined the phrenic nerve and respiratory function, so caution must be taken if we attempt to extrapolate findings to non-respiratory muscles. Functional movements involving the limbs are extraordinarily complex, as excitatory and inhibitory inputs to agonist and antagonist motoneurone pools must carefully coordinate to perform goal directed tasks. Interventions that alter O_2, CO_2 or monoamines are non-discriminatory and will likely cause widespread changes across motor pools. So if we expect to see changes in excitatory pathways to a motor pool due to an intervention, we should also be prepared to uncover changes in inhibitory pathways and the antagonist motor pool when performing functional movements.

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Additional information

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Supporting information

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