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Review Article

Enhancing neural activity to drive respiratory plasticity following cervical spinal cord injury

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ABSTRACT

Cervical spinal cord injury (SCI) results in permanent life-altering sensorimotor deficits, among which impaired breathing is one of the most devastating and life-threatening. While clinical and experimental research has revealed that some spontaneous respiratory improvement (functional plasticity) can occur post-SCI, the extent of the recovery is limited and significant deficits persist. Thus, increasing effort is being made to develop therapies that harness and enhance this neuroplastic potential to optimize long-term recovery of breathing in injured individuals. One strategy with demonstrated therapeutic potential is the use of treatments that increase neural and muscular activity (e.g. locomotor training, neural and muscular stimulation) and promote plasticity. With a focus on respiratory function post-SCI, this review will discuss advances in the use of neural interfacing strategies and activity-based treatments, and highlights some recent results from our own research.

Contents

1. Introduction

The formation and retention of functionally relevant neuronal connections during development is driven in part by motor and sensory activity. Increased and/or repetitive activity in mature pathways

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strengthens existing neuronal circuits (increasing synaptic and dendritic growth), refines and prunes irrelevant connectivity through synaptic competition, and can promote the recruitment of additional neurons into these pathways while preserving selectivity. Accordingly, these neuroplastic changes can be harnessed for therapeutic gain. Treatments designed to stimulate neural activity can contribute to the formation of new neural pathways and repair of those that are damaged, ultimately resulting in improved function following spinal cord injury (SCI). Strategies to drive neural activity can be separated into those using electrical stimuli ('neural interfaces' (NI's): functional electrical stimulation, epidural stimulation, transcranial magnetic stimulation) and physical stimuli ('activity-based therapies' (ABTs): rehabilitation, locomotor training). NIs and ABTs may be structured to either engage local circuits and musculoskeletal subsystems (e.g. a specific muscle and reflex) targeted in the therapy, or to engage broader system function (e.g. locomotion as a whole). Both approaches are becoming widely recognized as effective, clinically-viable means of reactivating neural circuitry that might otherwise remain inactive following SCI. For instance, electrical stimulation of the spinal cord caudal to a SCI (e.g. using epidural stimulation and intraspinal microstimulation) can restore sufficient activity to denervated spinal motor networks en masse to evoke not only simple tasks such as stance, but also more complex patterned limb movements (Bamford and Mushahwar, 2011; Tator et al., 2012), or to regulate specific synergies and phases of locomotion (Giszter, 2015; Wenger et al., 2016). With some parallels to electrical stimulation, physically increasing activity with exercise or rehabilitation also activates neural circuits in a localized or more general fashion. Persistence of this physical training strengthens the muscles being used, stimulates afferent feedback and drives contextual neural plasticity. For example, treadmill training can harness beneficial neuroplastic changes to promote lasting functional improvement in people with SCI (Harkema, 2001). More recently combinations of NIs and ABTs (e.g. epidural stimulation and locomotor training) have been shown to act synergistically for further enhancement of function (Hsieh and Giszter, 2011).

While historically the focus has been on improving locomotor recovery, there is growing appreciation for how stimulating neural activity can be used to treat non-locomotor impairments (bladder dysfunction, pain, spasticity, and respiration). Autonomic and segmental sensory motor function is likely integrated at the circuit level, but little effort has been made to investigate these interactions. General system effects of neural motor activity are likely more pervasive than they were previously considered. Building upon recent clinical findings and ongoing experimental studies, the present review discusses how strategies for stimulating neural activity can be used therapeutically to enhance respiratory function following cervical SCI.

2. Respiration post-SCI

Motoneurons innervating respiratory muscles are distributed throughout the cervical, thoracic and lumbar spinal cord (innervating the diaphragm, intercostals and abdominals, respectively) (Lane, 2011). Thus, SCI at any of these levels can affect respiratory function. Injuries at thoracic and lumbar levels can compromise the motor pathways controlling the intercostal and abdominal muscles. While thoracic and lumbar level injuries have little impact on inspiratory function (largely mediated by the phrenic motor system and diaphragm), they can produce deficits in respiratory–related behaviors (e.g. sneezing, coughing). Furthermore, impaired airway clearance can contribute to life-threatening secondary respiratory infections (Baydur and Sassoon, 2010).

The most severe respiratory deficits arise following cervical SCI, which not only partially or completely denervates respiratory circuitry at thoracic and lumbar spinal levels, but directly compromises the phrenic motor circuitry. Spinal phrenic motoneurons innervate the diaphragm, which is the most important respiratory muscle. Thus, injuries compromising phrenic motor function result in diaphragm paralysis/paresis, and typically necessitate assisted ventilation. Furthermore, cervical SCI denervates more caudal respiratory circuitry resulting in a combined inspiratory and expiratory dysfunction, impairing defensive respiratory-related behaviors (e.g. cough), and thereby increasing the risk of secondary complications (e.g. infection).

Despite these devastating outcomes, extensive research has shown some potential for respiratory plasticity and spontaneous functional recovery following cervical SCI. While the amount of recovery attributable to plasticity is limited, several studies have shown that onset and extent of plasticity can be therapeutically enhanced. Ongoing research is identifying new therapeutic targets that will promote respiratory plasticity and lasting recovery of breathing post-SCI.

3. Plasticity after cervical SCI

For the purpose of this review neuroplasticity can be defined as the ability of the nervous system to make anatomical and functional changes that lead to persistent alterations in sensory-motor function. These changes can be mediated by a range of factors, such as prior synaptic activity (e.g. activity-dependent learning), persistent physical activity (e.g. rehabilitative training), or injury (e.g. SCI). Furthermore, this plasticity can also occur 'spontaneously' (without external interference) following traumatic SCI and/or following therapeutic intervention (driven by external influences). An important goal for SCI treatments is that they either; i) do not impair spontaneously occurring, beneficial plasticity, ii) limit any detrimental aspects of plasticity (e.g. spontaneously occurring pain), or even more preferably, iii) act synergistically to enhance intrinsic neuroplasticity and optimize the extent of lasting functional improvement.

Following SCI, anatomical plasticity (e.g. reorganization of neuronal connections, activation of spared latent pathways) can lead to functional plasticity (e.g. restoration of activity in damaged pathways, increased activity in spared pathways to compensate for damage, synaptic strengthening), and vice-versa. While the present review focuses on neuroplastic changes within the spinal cord post-injury, it should also be noted that plasticity from the peripheral nervous system (Mantilla and Sieck, 2009; Nicaise et al., 2012b) to supraspinal circuitry (Golder et al., 2001; Goshgarian, 2009) can occur post-SCI and may affect functional outcome. Even a localized event (e.g. SCI) can result in plasticity through the brain, brainstem, spinal cord, peripheral nerves and muscle (Bezdudnaya et al., 2014; Oza and Giszter, 2014, 2015; Raineteau and Schwab, 2001). Another important consideration is that neuroplastic changes do not always translate to functional improvements and may even result in erroneous and detrimental (maladaptive) functions (e.g. pain, spasticity) (e.g. Ferguson et al., 2012; West et al., 2015). With that in mind, the timing and 'dose' of any treatment must be carefully assessed to limit maladaptive effects and optimize repair and recovery.

Evidence for functional respiratory plasticity was first demonstrated over a century ago using a lateral C2 hemisection (C2Hx) (Porter, 1895), which has since become the most frequently used model of respiratory dysfunction and plasticity following SCI (Goshgarian, 2003; Hoh et al., 2013; Vinit and Kastner, 2009b; Warren and Alilain, 2014). This type of injury compromises direct (monosynaptic) projections from the ventral respiratory column in the medulla to ipsilateral phrenic motoneurons (Ellenberger and Feldman, 1988; Ellenberger et al., 1990; Keomani et al., 2014; Lane et al., 2009b; Lane et al., 2008; Vinit and Kastner, 2009a), and results in an ipsilateral hemidiaphragm paralysis (Fig. 1). Despite the extent of injury, acute partial recovery of phrenic and hemidiaphragm activity after C2Hx can be accomplished by a subsequent contralateral phrenicotomy (Goshgarian, 2003; Porter, 1895) or by inducing a respiratory stress such as asphyxia, hypoxia or hypercapnia (Golder and Mitchell, 2005; Lewis and Brookhart, 1951). This type of post-injury plasticity – known as the "cross-phrenic phenomenon" (CPP) – is attributed to activation of contralateral (spared), normally latent, bulbospinal pathways that cross the spinal midline below the injury (Fig. 1A) (Goshgarian et al., 1991; Moreno et al., 1992).