ABSTRACT

RESPIRATORY RECOVERY VIA ENDOGENOUS AND ELECTRICAL STIMULATION-INDUCED MECHANISMS FOLLOWING CERVICAL SPINAL CORD INJURY

Taylor C Holmes, PT, DPT

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Breathing is a complex neuromuscular behavior vital for the maintenance of life. Cervical spinal cord injury (cSCI) disrupts descending respiratory motor drive and can lead to profound breathing impairments. While a limited, endogenous recovery of respiratory function has been well described following cSCI, this work has predominantly utilized single sex investigations. Given that relatively few treatment options exist to address this respiratory insufficiency, a more complete characterization of respiratory recovery post-cSCI is necessary for the development and evaluation of rehabilitative protocols. Diaphragm pacing (DP) is an emerging clinical intervention that utilizes electrical stimulation of the diaphragm muscle to combat the deleterious effects associated with standard treatment and has shown potential as a rehabilitative intervention. However, widespread use of DP as a rehabilitative modality has been limited by a lack of controlled studies. Thus, the purpose of this dissertation was to describe both the endogenous and electrical stimulation-induced recovery of respiratory function in a rodent model of cSCI. First, to provide a more complete characterization of endogenous respiratory recovery post-cSCI, we utilized physiological, functional, and morphological analyses in male and female rodents through chronic post-injury stages. This work is the first to show subtle, sex-based differences in respiratory recovery at the subacute to chronic stages following cSCI. Given that rehabilitative interventions commonly occur within these stages, these findings highlight the need to consider sex as a variable in the evaluation of rehabilitative protocols. Subsequently, we investigated the rehabilitative potential of repeated, daily DP in awake, behaving rodents following cSCI. We observed both a short- and long-lasting ventilatory plasticity with the use of DP following cSCI. Importantly, long-lasting effects were only observed in male rodents. Additional examination of spinal tissue reveals DP-induced changes to neuroinflammatory profiles and spinal activation patterns in these male animals. Finally, a preliminary mechanistic investigation suggests that phrenic afferents are necessary for these DP-induced changes, as the effects are attenuated with the use of cervical dorsal rhizotomy. Collectively, this work provides the first controlled investigation into the rehabilitative potential of DP in awake, behaving rodents and further emphasizes the importance of considering sex in future investigations post-cSCI.