Toward Precision Medicine After SCI: The Genetic Influence of ApoE on Respiratory Motor Plasticity

Lydia Hager [1] • *Rachel Maggard* [1] • *Daimen Stoltz* [1] • *Kyle Ritter* [1] • *Brittany Turba* [1] •

Warren Alilain, PhD [1]

[1]Neuroscience, University of Kentucky

Spinal cord injury (SCI) at the cervical level interrupts bulbospinal neurons that project from the medulla to the phrenic motonucleus at C3-C5. Since diaphragmatic innervation originates from the phrenic motonucleus, cervical spinal cord patients often experience breathing impairment. Thus far, therapies aimed at promoting recovery through regeneration of severed axons or plasticity of spared but weakened tracts have been met with little clinical success. To address this deficiency, we propose that an important variable has largely been ignored in the search for methods to promote this recovery. This variable is the genetic diversity among the human SCI population. Genetic factors contributing to plasticity after SCI could significantly influence respiratory motor recovery. The ApoE gene is known to influence risk of Alzheimer's Disease, with the E4 allele representing a greatly increased risk of AD. In the few studies investigating the ApoE gene's impact in SCI, the ApoE4 allele has been associated with decreased motor recovery and longer rehabilitation periods following SCI in the human population. In vitro studies have found that E4 interferes with mitochondrial function and reduces the expression of glutamate receptors on the surface of neurons. Therefore, we have begun to investigate the impact of the various ApoE alleles on respiratory motor plasticity using both in vitro and in vivo models. In the present study, long term facilitation (LTF) was induced in rats in the presence of human ApoE3 and E4 proteins to determine their influence on plasticity in vivo. In animals that received E4, LTF was abolished and immunohistochemistry revealed that fewer glutamate receptors were localized in synapses. Additional studies have focused on mitochondrial energetics in cells in the presence of both E3 and E4 in order to elucidate a potential mechanism for the inhibitory effects of ApoE4 on neural regeneration and plasticity. The human genetic component of neural plasticity, which has thus far been overlooked, could provide insight into how best to approach treatment for the SCI population and initiate a shift towards personalized medicine.