Spinal Cord Injuries

Identifying Therapeutic Targets to Aid in the Recovery of Respiration Post-cervical Spinal Cord Injury

Cervical spinal cord injury (SCI) results in a range of long-term deficits, one of which is impaired respiration, which results in a need for assisted ventilation. Impairment is largely due to damage to the phrenic neural pathways, the connections between neurons that controls the diaphragm. Through a series of studies, researchers at Drexel University (Philadelphia, PA) investigated changes in the phrenic circuitry after SCI and explored potential therapeutic targets for improved respiratory function among the cervical SCI population.

Specific spinal neurons known as interneurons have been shown to promote changes in respiratory pathways. In the first study, the team investigated whether transplantation of interneurons may improve respiratory outcomes after SCI. Rats with upper SCIs received grafts of dissociated, developing spinal cord tissue (tissue abundant in interneurons) from a healthy rat pup. After one month, neurons from the donor had formed connections with host phrenic neurons. Connections from host neurons onto donor neurons were also formed. At this early stage, the anatomical and functional results varied across individuals. However, the results demonstrate significant plasticity of the phrenic circuitry, providing an attractive therapeutic target to aid in weaning individuals off artificial ventilation (*Spruance et al., 2018*).

As demonstration of this therapeutic potential, the team stimulated the tissue around the spinal cord at the level of the phrenic neural center in a rat model of cervical SCI to stimulate breathing and to investigate methods for pacing this circuit (*Bezdudnaya et al., 2018*). High frequency stimulation of the C4 spinal segment was able to maintain breathing. Stimulation also facilitated changes in the timing of nerve signaling suggesting that it may be a potential target for pacing phrenic activity.

Additional research from this group investigated factors contributing to spontaneous recovery of diaphragm function following SCI (*Bezdudnaya et al., 2018; Hormigo et al., 2017*). It was determined that anesthesia attenuates recovery, suggesting that the N-methyl-D-aspartate (NMDA) neuronal receptors that are suppressed by anesthesia are critical for respiration and are potential therapeutic targets (*Bezdudnaya et al., 2018b*).

Therapies acting on the targets identified in this work could aid in weaning patients with spinal cord injury and resulting respiratory dysfunction off an artificial ventilation system.

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