Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of regenerative medicine

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Lithium for the treatment of ventral root avulsion

Evaluation of: Fang XY, Zhang WM, Zhang CF, Wong WM, Li W, Wu W, Lin JH. Lithium accelerates functional motor recovery by improving remyelination of regenerating axons following ventral root avulsion and reimplantation. *Neuroscience* 329, 213–225 (2016).

Complete or partial avulsion of the brachial plexus due to trauma or obstetric complications is commonly seen. Motor neuron death and paralysis of the muscles are ultimately involved. The interface of the central and the peripheral nervous system is complicated and avulsions usually involve both systems. Surgical procedures in animal models along with growth factor addition have proven to be difficult and incomplete. Functional recovery is often poor. There is a limit to the number of innervation of the motor units that target the muscle, which typically leads to atrophy. Combination strategies have involved drug treatment but with little improvement. The researchers of the current manuscript decided to look at a widely used long-term mood stabilizer, lithium, as a potential treatment due to its proven evidence of improvement of acute brain injuries.

Fang *et al.* utilized an avulsion model in rats and dissected an avulsed the C5–7 dorsal and ventral roots and replanted the C6 ventral root to the cut edge. They utilized a grooming test, Terzis grooming test, to determine the functional effects of treatment. One day after surgery, all animals

had a Terzis grooming test score of 0, which indicates complete loss of motor function. The improvements in the lithium-treated animals were seen 4 weeks after surgery; however, no functional recovery was seen in control groups until 6 weeks postsurgery. Improvements in the lithium-treated groups were demonstrated up to 11 weeks postsurgery. Immunostaining indicated at 6 weeks postsurgery; the lithium and control groups had little improvement in the motor neuron death. On the other hand, at 12 weeks postavulsion, the animals treated with lithium had a higher incidence of motor neuron survival. Importantly, motor axon regeneration was also assessed and was completed by doing fluorogold labeling. The researchers discovered that 6 weeks postavulsion, there was a decrease in the number of cells, however, at later time points, and the lithium-treated animals had more fluorogold-labeled axons. Myelination was also assessed as an indicator of recovery with lithium treatment. Fang *et al.* utilized electron microscopy technology to achieve results. The contralateral side of the nerve in both groups contained large thick myelin sheaths and a few small axons. 6 weeks after surgery, the axons on the nerve decreased significantly. The lithium-treated animals showed an increased number of axons in addition to increased number of large-diameter axons. Interestingly, the researchers also determined in later time points, lithium-treated animals had more axons with compacted myelin sheaths in addition to thicker myelin sheath and later more myelin-related gene expression. Upon

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a more intense review, the researchers were able to prove that the myelin sheaths were also thicker in the lithium-treated animals at earlier time points. Muscle atrophy is a common downstream pathology associated with avulsion due to lack of denervation. The extent of muscle atrophy was reduced in animals treated with lithium compared with the vehicle-treated animals. Immunohistochemistry also indicated the motor end plates to be more intact in the lithium-treated animals. Furthermore, functionality in using stimulus assessments indicated that the lithium-treated animals had shorter latency and higher peak-to-peak amplitudes.

The complicated interface of central and peripheral nervous systems was tackled by the researchers of this paper. It was important to assess functionality in addition to cellular aspects of the model. The treatment

of lithium more than likely preserved the axons still present within the avulsion, so it may work as a treatment option for some injuries. Downstream signaling effectors and long-term effects need to be researched further. This work highlights the benefits of utilizing approved therapies for other pathological conditions.

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