Regeneration Can be Achieved after Chronic Spinal Cord Injury

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Scientists at the University of California, San Diego School of Medicine report that regeneration of central nervous system axons can be achieved in rats even when treatment is delayed more than a year after the original spinal cord injury.

"The good news is that when axons have been cut due to spinal cord injury, they can be coaxed to regenerate if a combination of treatments is applied," said lead author Mark Tuszynski, MD, PhD, professor of neurosciences and director of the Center for Neural Repair at UC San Diego, and neurologist at the Veterans Affairs San Diego Health System. "The chronically injured axon is not dead."

While there are more than 10,000 new spinal cord injuries annually in the United States, nearly 250,000 patients are living in the chronic stages of injury. Yet nearly all previous spinal cord injury studies have attempted to stimulate regeneration when treatment is begun almost immediately after injury - because, in part, scientists considered it very difficult to achieve regeneration at such long time points after injury. None had shown successful regeneration in the late, chronic stages.

Reporting in the October 29 issue of the Cell Press journal *Neuron*, the UC San Diego team demonstrated successful regeneration of adult spinal cord axons into, and then beyond, an injury site in the cervical spinal cord, the middle region of the neck. Treatment was begun at time periods ranging from six weeks to as long as 15 months after the original injury in rats.

A number of mechanisms create formidable barriers to regeneration of injured axons in chronic spinal cord injury. These include scar formation at the injury site, a partial deficiency in the intrinsic growth capacity of adult neurons, the presence of inhibitors to growth, and, sometimes, extensive inflammation. Chronically injured neurons show a loss of expression of regeneration-promoting genes, and there is progressive degeneration of spinal cord white matter beyond lesion sites - all contributing to a poor environment for axonal re-growth.

Even under ideal laboratory circumstances, axonal re-growth is complex, requiring a combination of three things: a cellular bridge in the lesion site; a nervous system growth factor to guide axons to the correct target; and a stimulus to the injured neuron that turns on regeneration genes. Using this combinatorial treatment, the research team achieved axonal bridging beyond the original lesion site in rats when treatment was delayed for up to 15 months after the original spinal cord injury. Animals lacking the full combination treatment did not exhibit axonal regrowth.

The scientists also conducted genetic studies to measure how broad sets of genes in cells can be activated when treatment is delayed after injury. They discovered that, despite considerable delays, most genes could still be turned on to support regeneration, indicating that a chronically injured cell can still be "primed" to grow.

The studies were done in sensory systems that relay the sense of touch from the body to the brain. In ongoing studies, the scientists are testing these approaches for regenerating axons that control movement in chronically injured rats. "Our findings indicate that there is potential for promoting repair of the injured spinal cord even in chronic stages of injury," said Tuszynski. "While the regenerating axons grow for relatively short distances, even

this degree of growth could be useful. For example, restoration of nerve function even one level below an injury in the neck might improve movement of a wrist or hand, providing greater quality of life or independence."

Contributors to the study include first authors Ken Kadoya and Shingo Tsukada, UCSD Department of Neurosciences; Paul Lu, UCSD Neurosciences and Veterans Affairs Medical Center, San Diego; Giovanni Coppola and Dan Geschwind, UCLA Department of Neurology; Marie Filbin, Hunter College, NY; and Armin Blesch, UCSD Department of Neurosciences. The study was funded by the National Institutes of Health, the Veterans Administration, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, and the Bernard and Anne Spitzer Charitable Trust.

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