

Spinal cord bridge bypasses injury to restore mobility

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The body's spinal cord is like a super highway of nerves. When an injury occurs, the body's policing defenses put up a roadblock in the form of a scar to prevent further injury, but it stops all neural traffic from moving forward.

Researchers from Case Western Reserve University, Drexel University and the University of Arkansas bypassed this roadblock in the spinal cord. First, the researchers regenerated the severed nerve fibers, also called axons, around the initial large lesion with a segment of peripheral nerve taken from the leg of the same animal that suffered the spinal injury. Next, they jump started neural traffic by allowing many nerve fibers to exit from the end of the bridge. This was accomplished, for the first time, by using an enzyme that stopped growth inhibitory molecules from forming in the small scar that forms at the exit ramp of the bridge, where it is inserted into the spinal cord on the other side of the lesion. This allowed the growing axons to reconnect with the spinal cord.

Jerry Silver, a professor of neurosciences at the Case School of Medicine, was senior author among the researchers reporting in the *Journal of Neuroscience* article, "Combining an Autologous Peripheral Nervous System 'Bridge' and Matrix Modification by Chondroitinase Allows Robust Functional Regeneration beyond a Hemisection Lesion of the Adult Rat Spinal Cord." The other researchers were John Houle, the lead author, and Veronica Tom (a Case alum) from Drexel University College of Medicine; and Gail Wagoner and Napoleon Phillips from the University of Arkansas.

The researchers employed a combination of two strategies--one old and one new--in efforts to regenerate nerves in the spinal cord and restore movement, said Silver.

For more than 100 years, researchers have used grafts of peripheral nerves from the rib area or parts of the leg. While peripheral nerves can be used successfully as grafts in the limbs, spinal cord injuries put up defenses called inhibitory chondroitin sulfate proteoglycans that create molecular guardrails within scars at the lesion site. These scars act as a barrier to regenerating axons and result in loss of the ability to breathe or move arms or legs, depending upon the injury site.

Silver said the medical community also assumed that the cut axon tips died when they hit the scar wall. In prior research in his lab by his graduate student, Tom, it was discovered that axons are alive and continue to attempt to grow for years. Silver describes them as "trucks stuck in mud going no where." It also explains why some people gain some movement back or come out of comas after many years as the nerve fibers sprout through weakened or remodeled areas of the scar.

About 16 years ago, Silver also made another find that proteoglycans, a sugary protein, is present at the site of spinal cord lesions. He also knew that a particular enzyme from the bacteria *Proteus vulgaris*, called chondroitinase, might dismantle the proteoglycans by clipping their sugar branches, thereby preventing the scar wall from building.

In a National Institutes of Health-supported animal study, 12 rats had spinal injuries at the cervical level 3 (C3) that resulted in impaired motor functions to their right side limbs. The animals had trouble moving, climbing or grooming.

Combining the old with the new, the researchers grafted a 1.5 centimeter piece of the tibial branch of the sciatic nerve to the C3 area of the spinal

cord and allowed the nerve fibers to grow and regenerate over three weeks. .

At approximately two and a half weeks into the new nerve growth, Houle implanted a small pump that delivered a steady dose of chondroitinase to a new incision site near C5 where the researchers hoped to reconnect the other end of the bridge to the spinal cord, but also prevent further scarring. They also primed the newly re-grown axons for rapid regeneration by clipping their ends.

Silver said this method resulted in approximately 20 percent of the nerve fibers leaving the bridge and reconnecting with the spinal cord. It brought about markedly improved mobility for the seven rats given the chondroitinase treatment.

A control group of five rats underwent the same procedure. Instead of the chondroitinase, they were given a saline solution. None showed any nerve growth out of the bridge or improvement in their limbs.

To test whether something other than regeneration was at work in restoring movement, the neural bridges were severed and the rats lost all movement gained from the combination of treatments. This provides the most conclusive evidence to date that severed nerve fibers in the spinal cord can, in fact, regenerate for long distances and establish proper functional connections.

Silver said if the method is perfected and successful with primates, it could go to human trials within a relatively short time.

His next step is a neural bridge that would help quadriplegics, who are unable to breathe without assistance, move their diaphragms on their own. In future animal studies he plans to undertake nerve grafts from the leg to bridge the area of the spinal cord that controls breathing.

"While this was one small step for a rat, it was one giant leap for man," said Silver.

Source: Case Western Reserve University

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