

In reversing motor nerve damage, time is of the essence

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When a motor nerve is severely damaged, people rarely recover full muscle strength and function. Neuroscientists from Children's Hospital Boston, combining patient data with observations in a mouse model, now show why. It's not that motor nerve fibers don't regrow -- they can -- but they don't grow fast enough. By the time they get to the muscle fibers, they can no longer communicate with them.

The study, published in the November issue of the [Journal of Clinical Investigation](#) (online October 3) has immediate implications for patients with [motor nerve](#) injuries, including carpal tunnel syndrome, cubital tunnel syndrome, nerve damage caused by surgery and brachial avulsion injuries: Time is of the essence in repairing [nerve damage](#).

"There's a clock ticking, and if you're too late, the muscle cannot be functionally reactivated," says Clifford Woolf, Ph.D, senior investigator and director of the Program in Neurobiology and F.M. Kirby Neurobiology Center at Children's Hospital Boston. "If there's muscle weakness, waiting six months to see if it gets better or worse before intervening may not be the best idea."

Studying mice with sciatic nerve injury, Woolf and colleagues found that there's a limited [time window](#) in which [nerve fibers](#), or axons, must regenerate and extend toward the muscle, re-forming the junction known as a synapse. If this window is missed, and the [muscle fibers](#) have gone too long without stimulation, the axon is actually inhibited from going the final distance to form a synapse with them.

In mice, the window for recovering [nerve function](#) was about 5 weeks. When the nerve was simply crushed, the mice were able to stay within this window and recover motor function, because the axons grew quickly. But when the nerve was completely severed, axons were slower to begin growing, so missed the window, the team found.

The precise window for motor recovery in humans still isn't known, but a review of data from 136 patients with carpal tunnel syndrome and 20 with cubital tunnel syndrome (a compression injury of the ulnar nerve in the elbow) showed that the shorter the period from onset of symptoms to surgery, the greater the degree of motor recovery. In the patients with cubital tunnel syndrome, muscle tests yielded an average functional score of 4 (on a scale of 0 to 5) among those who had decompression surgery within 10 months of injury, versus just 0.5 among those having surgery more than 10 months after injury, a highly statistically significant difference.

The study highlights the fact that achieving nerve regeneration isn't the whole story. The next big challenge is getting the regenerated axon to function. Woolf and colleagues' mouse experiments suggest two approaches.

One is to speed up axon growth -- which the investigators accomplished by turning on the gene for human heat shock protein 27 (Hsp27). This protein, naturally secreted in response to injury, is produced right at the leading edge of the axon, they found, and primes it to grow and extend.

Mice with Hsp27 turned on had greater axon growth -- the distance the fibers extended within 72 hours was almost doubled. They were able to recover motor function in their paws even when their sciatic nerve was completely severed, whereas the paws of mice without Hsp27 remained paralyzed and showed muscle atrophy. In the future, Woolf and colleagues will set up a drug screen and test for compounds that increase

levels of Hsp27 without having to do genetic manipulations.

A second possible approach to enhancing motor recovery is to block the signals that prevent "latecomer" [axons](#) from forming synapses with the muscle. In further work, Woolf hopes to find out what those inhibitory signals are, and the team has already started screening for compounds that might counter them.

Provided by Children's Hospital Boston

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