

Stem Cell Mix Helps Paralyzed Rats Walk

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A complex combination of treatments, including stem cells and growth factors, can heal damaged neural circuits, allowing partially paralyzed rats to walk. These findings represent a significant step forward in regenerative medicine, providing new treatment possibilities for Amyotrophic Lateral Sclerosis (ALS) and other neurodegenerative diseases, as well as some types of spinal-cord injury.

"This work is a major stepping-stone to human application of stem-cell transplant approaches," says Hans S. Keirstead, co-director of the Stem Cell Research Center at the University of California, Irvine. He says that the ability to grow new neural fibers out of the spinal cord "renders transplantation approaches to repair realistic."

Previous research has shown that cell transplants and other treatments can help paralyzed rodents walk. But those experiments have focused mainly on repairing local damage within the spinal cord. They could help patients whose motor neurons -- cells carrying messages from brain to spinal cord -- remain intact after injury or disease.

In contrast, the current study, conducted by a team of scientists at Johns Hopkins University, focused on a longer-distance repair problem. It is the first study to show that newly grown nerve fibers can emerge from the spinal cord, extend all the way to the muscle, then form functional connections with muscle. This feat is particularly important for ALS and other disorders characterized by the loss of motor neurons. "Some may have thought this was a

bridge you can't cross," says David Owens, research director at the National Institutes of Neurological Disorders and Stroke, which sponsored the study.

Researchers caution that the work is just a first step, and that human trials are likely several years away. Indeed, the findings highlight just how complex spinal injuries and neurodegenerative disorders are and how complicated successful treatments are likely to be.

The spinal cord is a precisely organized neural circuit, with one set of neurons connecting the brain to the spinal cord and another set joining the spinal cord to muscles. The nervous system has evolved several mechanisms to maintain the circuit's tight structure -- and that strict regulation presents a serious obstacle for scientists who want to rewire the system after damage or disease.

To overcome these hurdles, Douglas Kerr and his team at Johns Hopkins took clues from the developing nervous system. "In the developing nervous system, there are signposts along the way that tell every cell and every wire where to go and what to do," says Kerr.

The researchers first took embryonic stem cells and transformed them in a dish into motor neurons. They then transplanted the cells into the spinal cord, along with a mix of growth factors normally present during development, to help the new cells survive and to encourage surrounding cells to make connections with the transplanted ones. The scientists also added two chemicals known to overcome the inhibitory forces that normally keep nerve fibers from growing out of the spinal cord.

In order to get the newly sprouted axons to span the lengthy gap from the spinal cord to the muscle, the researchers injected neural stem cells, which produce a nerve growth stimulator called GDNF.

When delivered to the target muscles, the GDNF acted as a powerful attractor to the growing motor neurons, allowing them to grow toward the muscle, and, most importantly, to make functional neuromuscular connections. The final result: the disrupted neural circuit is reconnected, allowing the brain to send messages to the muscle.

According to the new findings, 11 out of 15 mice that received the full battery of treatments regained some motor function, moving around their cages more easily. For example, in one mouse with roughly 4,100 new motor neurons transplanted to its spinal cord, the nerve fibers of approximately 200 of those neurons exited the spinal cord, and 120 of those reached the skeletal muscle, forming typical neuromuscular connections.

In addition, Kerr and team discovered that the mice needed every element of the regimen for the best recovery. In mice who received only a subset of treatments, neurons either died or did not reach their target, and the mice showed little improvement in movement. The findings were published today in the *Annals of Neurology*.

"Getting neurons to be functional is a big plus and an exciting step forward," says Stephen M. Strittmatter, a neuroscientist at Yale University School of Medicine, who has done seminal work uncovering the inhibitory forces at work in the spinal cord.

Most previous research in spinal-cord damage has focused on encouraging existing neurons to grow and form new connections with the spinal cord or on giving surviving neurons new insulation, which is often damaged in spinal injury, preventing neural signals from being transmitted. Such results have important applications for many types of spinal-cord injury, where motor neurons still function but must be reconnected to the cord.

Kerr's experiments tackled a different problem, using embryonic stem cells to create an entirely new connection between the spinal cord and muscle. In addition to ALS, the findings present a potential avenue of treatment for spinal muscular atrophy, a degenerative disease that can be fatal in infants, as well as some types of multiple sclerosis and spinal-cord injury, which all show loss of motor neurons. Kerr's regimen could ultimately be combined with other treatments, such as cell transplants to replace myelin sheaths. "Used in combination, these techniques could really have promise for people with complex spinal-cord injuries," says Michael Fehlings, a neuroscientist and neurosurgeon at the University of Toronto.

In fact, scientists say variations of the technique could ultimately have applications for a wide range of neurological disorders, including Parkinson's disease. "We've figured out a boilerplate recipe for how to reconnect disconnected cell populations," says Kerr.

The team is now planning similar tests in pigs. Studies in larger animals are necessary to make sure that the new neurons can grow the lengths needed for the treatment to work in humans. If those experiments are successful, says Kerr, human clinical trials could occur within five years.

But clinical testing is likely to be a feat in itself. "This is a very complicated strategy, and it's going to be challenging to translate that into clinical trials," says Mary Bunge, a spinal-cord expert who works at the Miami project to cure paralysis at the University of Miami. "But they got good results and maybe that'll give us new ideas to test."