

First oral drug for spinal cord injury improves movement in mice

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An experimental oral drug given to mice after a spinal cord injury was effective at improving limb movement after the injury, a new study shows.

The compound efficiently crossed the blood-brain barrier, did not increase pain and showed no <u>toxic effects</u> to the animals.

"This is a first to have a drug that can be taken orally to produce functional improvement with no <u>toxicity</u> in a <u>rodent model</u>," said Sung Ok Yoon, associate professor of molecular & cellular biochemistry at Ohio State University and lead author of the study. "So far, in the spinal cord injury field with rodent models, effective treatments have included more than one therapy, often involving invasive means. Here, with a single agent, we were able to obtain functional improvement."

The small molecule in this study was tested for its ability to prevent the death of cells called oligodendrocytes. These cells surround and protect axons, long projections of a nerve cell, by wrapping them in myelin. In addition to functioning as axon insulation, myelin allows for the rapid transmission of signals between nerve cells.

The drug preserved oligodendrocytes by inhibiting the activation of a protein called p75. Yoon's lab previously discovered that p75 is linked to the death of these specialized cells after a spinal cord injury. When they die, axons that are supported by them degenerate.



"Because we know that oligodendrocytes continue to die for a long period of time after an injury, we took the approach that if we could put a brake on that cell death, we could prevent continued degeneration of axons," she said. "Many researchers in the field are focusing on regeneration of neurons, but we specifically targeted a different type of cells because it allows a relatively long therapeutic window."

An additional benefit of targeting oligodendrocytes is that it can amplify the therapeutic effect because a single oligodendrocyte myelinates multiple axons.

A current acute treatment for humans, methylprednisolone, must be administered within eight but not after 24 hours after the injury to be effective at all. An estimated 1.3 million people in the United States are living with spinal cord injuries, experiencing paralysis and complications that include bladder, bowel and sexual dysfunction and chronic pain.

The experimental drug, called LM11A-31, was developed by study coauthor Frank Longo, professor of neurology and neurological sciences at Stanford University. The drug is the first to be developed with a specific target, p75, as a potential therapy for spinal cord injury.

The research is published in the Jan. 9, 2013, issue of *The Journal of Neuroscience*.

Researchers gave three different oral doses of LM11A-31, as well as a placebo, to different groups of <u>mice</u> beginning four hours after injury and then twice daily for a 42-day experimental period. The scientists analyzed the compound's effectiveness at improving <u>limb movement</u> and preventing myelin loss.

The <u>spinal cord injuries</u> in mice mimicked those caused in humans by the application of extensive force and pressure, resulting in loss of hind-



limb and bladder function and experimentally calibrated baseline difficulty in walking and swimming.

The researchers determined that the mice did not experience more pain than the placebo group at all the doses tested, suggesting that LM11A-31 does not worsen nerve pain after spinal cord injury.

Analysis showed that the extent of myelin sparing was dependent on the dose of the drug. Each dose -10, 25 or 100 milligrams per kilogram of body weight - led to increasing myelin sparing, with the highest dose demonstrating the greatest effect.

The injury in the animals caused a loss of about 75 percent of myelinated axons in the lesion area in the placebo group. This loss was reduced so that myelinated axons reached more than half of the normal levels with LM11A-31 at 100 mg/kg. That was correlated with about a 50 percent increase in surviving oligodendrotcytes compared to those in the placebo group, Yoon said.

In behavior tests, only the highest dose of the compound led to improvements in motor function. Mice were tested in both weightbearing and non-weight-bearing activities over the 42 days to evaluate their functional recovery.

Mice receiving the highest dose could walk with well-coordinated steps. In swimming tests, scientists saw similar improvements, with mice receiving the highest dose most able to coordinate hind-limb crisscross movement. The other treatment groups exhibited difficulty in walking and swimming.

Yoon said the findings may suggest that myelin sparing needs to reach a threshold of roughly 50 percent of normal levels before motor function improvements become measurable.



"The cellular analysis of the myelin profile detects small changes. Behavior is more complex, and we don't think functional behavior necessarily improves in a linear fashion," she said. "Still, these results clearly show that this is the first <u>oral drug</u> in <u>spinal cord</u> injury that works alone to improve function."

Provided by The Ohio State University

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