# New stroke therapy successful in rats

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People with impaired mobility after a stroke soon may have a therapy that restores limb function long after the injury, if a supplemental protein works as well in humans as it does in paralyzed rats.

Two new studies by UC Irvine biologists have found that a protein naturally occurring in humans restores motor function in rats after a stroke. Administered directly to the brain, the protein restores 99 percent of lost movement; if it's given through the nose, 70 percent of lost movement is regained. Untreated rats improve by only 30 percent.

"No drugs exist that will help a stroke after a few days. If you have a stroke, you don't have many treatment options," said James Fallon, psychiatry & human behavior professor and senior co-author of the studies. "Now we have evidence there may be therapies that can repair damage to a significant degree long after the stroke. It's a completely unexpected and remarkable finding, and it's worth trying in humans."

The studies, carried out by UCI postdoctoral researcher Magda Guerra-Crespo, chronicle the success of a small protein called transforming growth factor alpha, which plays critical tissue-forming and developmental roles in humans from just after conception through birth and into old age.

"TGF alpha has been studied for two decades in other organ systems but never before has been shown to reverse the symptoms of a stroke," Guerra-Crespo said. No lasting side effects were observed.

In the first study, published in the journal Neuroscience, scientists sought to learn whether TGF alpha administered directly to the brain could help rats with stroke-induced loss of limb function, typically on one side - as is seen in humans.

When put inside a cylinder, healthy rats will jump up with both front legs, but stroke-impaired rats will use just one leg, favoring the injured side. When given a choice of directions to walk, impaired rats will move toward their good side.

One month after the study rats suffered an induced stroke (equal to about a year for humans), some were injected with TGF alpha. Within a month, they had regained nearly all their motor function, hopping up with both legs in the cylinder exercise and not favoring a side in the directional test. Rats that did not receive treatment improved just 30 percent.

Scientists examined the rats' brains and found that TGF alpha was stimulating neuron growth. First, it prompted adult stem cells in the brain to divide, creating more cells. Those cells then turned into brain cells and moved to the injured part of the brain, replacing neurons lost to the stroke. These new neurons, the scientists believe, helped restore motor function.

"It's becoming more and more clear that the brain is like any other organ: It has a lot of potential to regenerate," said Darius Gleason, a developmental & cell biology graduate student who worked on the study. "We are just emulating nature by giving a little nudge to what the brain is trying to do itself."

In the second study, appearing online Jan. 11 in the *Journal of* Stroke *& Cerebrovascular Diseases*, scientists placed TGF alpha in the rats' noses, simulating a nasal spray. They used a slightly different chemical version

of the protein to render it more stable on its journey to the brain. After a month, the injured rats had regained 70 percent of their function, indicating that the intranasal method also works well.

"We saw the same phenomena," Fallon said. "It wasn't as profound, but we still ended up with very significant behavioral improvements and the same regenerative anatomical process."

Provided by University of California - Irvine