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Improved recovery of motor function after stroke

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After the acute treatment window closes, the only effective treatment for stroke is physical/occupational therapy. Now scientists from Children's Hospital Boston report a two-pronged molecular therapy that leads to significant recovery of skilled motor function in a rat model of stroke. Their findings are reported April 20 in the *Journal of Neuroscience*.

By combining two molecular therapies—each known to promote some recovery on its own—the researchers achieved more nerve growth and a greater recovery of motor function than with either treatment alone. One therapy, inosine, is a naturally-present molecule that promotes nerve growth; the other is NEP1-40, an agent that counteracts natural inhibitors of nerve growth.

"When you put these two together, you get much stronger growth of new circuits than either one alone, and very striking functional improvements," says senior author Larry Benowitz, PhD, of the Children's Department of Neurosurgery.

Strokes in humans often damage the motor cortex on one side of the brain, interfering with skilled motor functions on the opposite side of the body. Led by Laila Zai, PhD, a postdoctoral fellow in Benowitz's lab and the study's first author, the researchers modeled this scenario by inducing strokes on one side of the rats' brains—specifically in a part of the motor cortex that controls forelimb movement. They then examined the rats' ability to perform a skilled reaching task—retrieving food—with the forelimb on the opposite side.

After 3 to 4 weeks, rats treated with both inosine and NEP1-40 could perform the task—which required coordinated movements of the paw and digits—with success rates equivalent to those before the stroke. Benowitz likens the complexity of this task to a person eating with utensils or operating a joystick.

Benowitz has three issued US patents and several US and foreign patent applications pending for the use of inosine to treat stroke, spinal cord injury and traumatic brain injury, and a pending patent application for the inosine/NEP1-40 combined treatment of CNS injury. Earlier studies from his lab, including one published in 2002 and another published last year, demonstrated that inosine encourages nerve fibers to grow from the uninjured side of the brain into regions of the spinal cord that have lost nerve fibers due to stroke. This compensatory rewiring of neural circuits was matched by functional improvements. A separate 2007 study from the University of Cambridge also found that inosine promotes recovery of skilled motor function following traumatic brain injury in rats.

Inosine works by activating a key regulator of nerve growth (an enzyme known as Mst3b). It has a history of safe usage in humans—it is widely available as a nutritional supplement, and is currently being investigated in clinical trials for the treatment of multiple sclerosis and Parkinson's disease.

NEP1-40 complements inosine's effects by counteracting molecules outside of nerve cells that inhibit nerve growth. Specifically, it blocks signaling through the Nogo receptor, shown by a number of studies to promote the rewiring of neural circuits and to improve functional recovery after stroke.

Benowitz believes circuit rewiring is a promising approach to treating stroke because that is what is thought to underlie the recovery that happens naturally. People with strokes often do regain some function

that correlates with shifts in activity to the uninjured parts of the brain. In animal studies, these shifts in brain activity correlate with the growth of new branches from uninjured nerve fibers.

The researchers also found that inosine administered together with environmental enrichment (a model for physical/occupational therapy in humans) led to greater recovery of both nerve growth and motor function. "Physical/occupational therapy should always be part of the strategy," Benowitz says.

Provided by Children's Hospital Boston