Research in mice shows potential value of antidepressant in some stroke victims

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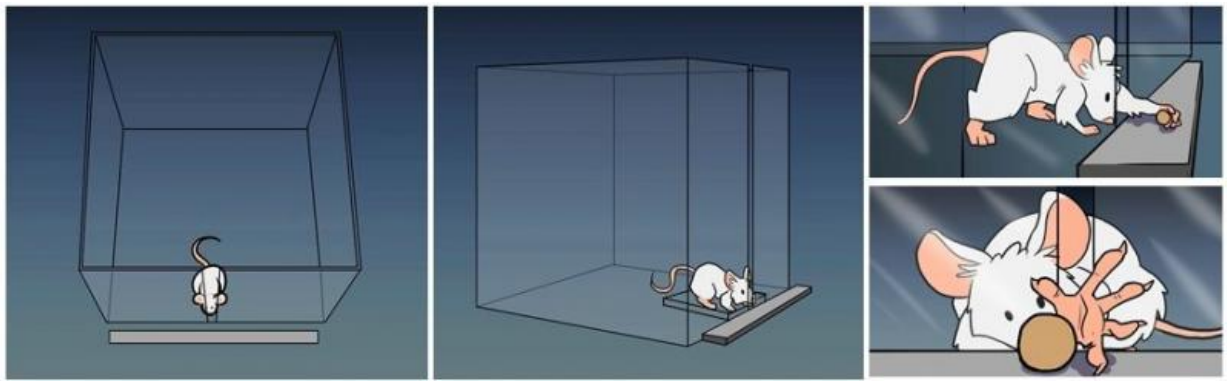

After a stroke, mice were tested on their ability to re-learn how to reach through an opening to grab a food pellet. Credit: Boone Snavely

Working with mice, researchers at Johns Hopkins have added to evidence that a commonly prescribed antidepressant called fluoxetine helps stroke victims improve movement and coordination, and possibly why.

Specifically, the researchers say, their experiments suggest the drug, often sold under the trade name Prozac, prolongs the time after a stroke during which physical therapy remains effective for recovering lost motor function.

The study, which may help explain the benefit of selective serotonin

reuptake inhibitors already seen in stroke patients, holds potentially great value for those too ill immediately after an ischemic stroke to start the intensive rehabilitation therapy needed to recover lost motor functions. Ischemic strokes are marked by the sudden loss of blood circulation to the brain caused by a clot.

"For rehabilitation to be effective, it needs to start as soon after a stroke as possible," says Steven Zeiler, M.D., Ph.D., assistant professor of neurology at the Johns Hopkins University School of Medicine and lead author of the study reported in the October issue of the journal *Stroke*. "But with this study, we've shown that in mice, we can extend the time period during which rehabilitative intervention has an effect on meaningful recovery."

An estimated 65 percent of stroke survivors experience some weakness or paralysis of their limbs, and difficulty in walking and moving due to the death of brain cells from lack of blood flow. Rehabilitation involves retraining other parts of the brain to take over and restore lost functions. Zeiler worked with John Krakauer, M.D., who directs the Brain, Learning, Animation and Movement Lab, to show that in mice, such behavioral efforts work best when they begin early and at high dosages. Numerous research studies have reached similar conclusions, Zeiler says.

For the current study, his team tested whether mice with induced strokes given fluoxetine would get the same recovery results even when rehab was delayed.

A 2011 study of patients who took fluoxetine after an ischemic stroke—called "Fluoxetine for motor recovery after acute ischemic stroke," or FLAME—suggested that the strategy could work. "We took the results of the success found in the FLAME study and reverse-engineered it to look at what fluoxetine may be doing," says Zeiler. "Nobody knows how fluoxetine worked in those patients' stroke

recovery—only that it did and it does."

The mouse model the researchers used involved training mice to do a task they don't normally do: reach through a slit to grab a food pellet. "As primates, we make this motion all the time," says Zeiler, "but quadrupeds, like cats, dogs and mice, aren't so good at it." Once the trained mice became good at it, the researchers induced a stroke in the motor area that affected the mice's ability to do that task.

To test whether the mice properly modeled human stroke patients, Zeiler started rehab with some of the mice immediately after the induced stroke. As with human stroke patients, early intervention made a difference: Those mice soon recovered the lost motor function. Mice for which rehab was delayed by a week showed incomplete recovery, gaining back a little less than one-half of their former ability.

"For patients," says Zeiler, "incomplete recovery means weakness or a loss of control in the affected body part or region." For the mice, it meant that they knocked the food pellet from the holder, dropped it or otherwise lost control of it.

When the researchers administered fluoxetine daily to the mice beginning 24 hours after inducing stroke, however, the mice recovered the ability to do the learned task even if they started rehab after a week's delay.

Zeiler emphasizes that the precise cause of fluoxetine's effect on stroke recovery is not yet known, but he says that after looking at brain tissue from his study's mice, he thinks the drug changed the way their brains responded to retraining. "We believe the drug is changing plasticity," says Zeiler, "changing the way individual neurons are responding to sensory input after the stroke."

"There are some who believe fluoxetine can reduce the amount of brain tissue that dies after a stroke," says Zeiler, but his team's findings do not bear that out. "In fact," Zeiler says, "there was more—not less—brain tissue death in the animals that got fluoxetine than in those that did not. We didn't predict that, but the fact that the animals actually got better—despite increased cell death—tells us that fluoxetine is having some pretty amazing effects."

"Time still matters; it's key," cautions Zeiler. The mice that fully recovered motor function were started on fluoxetine immediately after the induced stroke; if fluoxetine administration was delayed by one week after stroke, instead of 24 hours, the mice did not fully recover.

Like all drugs, Zeiler notes, fluoxetine can have negative side effects. Still, Zeiler says, stroke doctors at Johns Hopkins recommend it for stroke patients, especially those who suffer motor loss. "But it's not something that a patient would be prescribed forever," he adds.

Provided by Johns Hopkins University School of Medicine