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Lithium Eases Symptoms of Fatal Neurological Disorder

Studies in mice have shown that lithium, a drug widely used to treat mood disorders in humans, can provide relief from the crushing symptoms of a fatal brain disease, according to researchers at the Howard Hughes Medical Institute (HHMI) at the Baylor College of Medicine.

A team led by HHMI investigator Huda Y. Zoghbi did a series of experiments in mice that showed lithium, a psychiatric drug used to stabilize mood shifts, can ease the symptoms of spinocerebellar ataxia type 1, an inherited neurodegenerative disorder. Their research article was published on May 28, 2007, in the journal *Public Library of Science (PLoS) Medicine*.

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— **Huda Y. Zoghbi**

"The results are very exciting," said Zoghbi. "It's really hard to improve multiple symptoms (in a condition). Lithium seems to improve several in this case, not just one."

The new findings are important because they suggest it may be possible to use the drug to alleviate deteriorations in motor coordination, learning and memory manifested by the spinocerebellar ataxia. At present, treatments for the condition are limited and patients, who are usually diagnosed in their thirties or forties, experience a gradual decline in motor and memory function and die within a few years of onset of the disease.

"Now, we're very anxious to know if this is going to help patients with other ataxias," Zoghbi explained. Spinocerebellar ataxia type 1 is one of a group of nine human neurodegenerative diseases caused by a similar type of genetic defect.

Zoghbi stressed that lithium is no cure, but it could ease the debilitating symptoms of spinocerebellar ataxia and significantly improve the quality of life of patients. What's more, because the drug is already widely used in humans, the work of Zoghbi and her colleagues could be tested in humans far

faster than a new drug.

"What we really need to do now is a pilot study, just a small trial with a handful of patients to see if it's safe in this patient population. Because lithium is well known and has been used in humans for a long time, we wouldn't have to do as many safety trials," Zoghbi said.

Exploring lithium as a potential salve for neurodegenerative disorders makes sense, according to Zoghbi, because in past studies lithium has been shown to provide some protection for the brain in a variety of conditions. How the drug works to do that is unknown, but Zoghbi noted that lithium might affect gene transcription in multiple ways.

Zoghbi and her colleagues explored the effects of lithium on mice engineered to carry a mutant gene that causes a condition that precisely mimics human spinocerebellar ataxia type 1. The underlying genetic abnormality gathers steam as an animal ages and mediates protein interactions in the brain toxic to at least two types of cells. One group of affected cells helps coordinate movement and the other group of cells is involved in learning and memory. Patients gradually lose motor coordination, exhibit cognitive difficulties and eventually die as other neurons in the brain stem succumb to the disease.

Afflicted mice treated with lithium were subjected to a battery of tests to assess balance, coordination, learning and memory. Mice given lithium showed improved coordination, learning and memory even if therapy was started after the symptoms began.

Zoghbi and her group also documented improvement in the morphology of the specialized cells that conduct nerve impulses in the hippocampus, a region of the brain important for learning and memory.

Her group also looked at the effects of lithium on Purkinje cells, which are large, highly branched neurons that help direct motor activity. The drug had less of an effect on Purkinje cells, possibly because the cells are usually the first to succumb to the toxic effects of spinocerebellar ataxia type 1.

Damage to dendrites, the elegant branching arbors of brain cells that help conduct nerve impulses, is a hallmark of spinocerebellar ataxia, Zoghbi said: "Changes in dendrite patterning occur in several neurons with spinocerebellar ataxia. Dendrites start to disappear slowly with the onset of the condition and the Purkinje cells are the first to be hit, followed by hippocampal neurons."

Because the new study was conducted in mice engineered to have a more exaggerated form of the disease, and because mice age faster than humans, it might be that lithium could also exert its protective influence on Purkinje cells in human patients.

"We're hoping that in humans we can catch the Purkinje cells before they experience damage," she said.

Although lithium will not cure the disease and may not extend the lifespan of patients, its potential use as an agent to treat the symptoms of a devastating nervous system disorder is promising as the research suggests it can ease symptoms for patients who currently have no other therapeutic options.

"I'm cautiously optimistic," said Zoghbi. "Not everything that works in mice works in humans. But this is a safe drug already in use in humans and we've shown that it improves multiple symptoms in our model."

Co-authors of the *PLoS Medicine* article include Kei Watase, Jennifer R. Gatchel, Yaling Sun, Richard Atkinson, Ronald Richman and Chad Shaw, all of Baylor College of Medicine; Hidehiro Mizusawa of Tokyo Medical and Dental University; and Harry T. Orr of the University of Minnesota.