Lithium chloride slows onset of skeletal muscle disorder

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A new UC Irvine study finds that lithium chloride, a drug used to treat bipolar disorder, can slow the development of inclusion body myositis, a skeletal muscle disease that affects the elderly.

In the study by scientists Frank LaFerla and Masashi Kitazawa, mice genetically engineered to have IBM demonstrated markedly better motor function six months after receiving daily doses of lithium chloride, compared with non-treated mice. The muscles in treated mice also had lower levels of a protein that the study linked to muscle inflammation associated with IBM.

These data are the first to show that lithium chloride is a potential IBM therapy.

"Lithium chloride is an approved drug for treating humans. We already know it is safe and can be used by people," said LaFerla, professor of neurobiology and behavior at UCI and co-author of the study. "Given our findings, we believe a clinical trial that tests the effectiveness of lithium chloride on IBM patients should be conducted as soon as possible."

Results of the study appear online this month in the journal *Annals of Neurology*.

IBM is the most common skeletal muscle disorder among people older than 50. People with IBM experience weakness, inflammation and atrophy of muscles in their fingers, wrists, forearms and quadriceps. There is no cure for IBM, nor is there an effective treatment, according to the National Institutes of Health.

LaFerla, a noted Alzheimer's disease researcher, began studying IBM about 10 years ago after learning the disorders have similar tissue characteristics. In the brain, a buildup of phosphorylated tau protein leads to the development of tangles, one of the two lesions that are hallmarks of Alzheimer's disease. High phospho-tau levels also are present in IBM, though patients do not experience dementia or memory loss. In a previous study,

LaFerla found that lithium chloride reduced phospho-tau levels in mice genetically engineered to develop Alzheimer's disease.
LaFerla and his research team then wondered: Could lithium chloride also reduce phospho-tau levels and symptoms in mice with IBM?

First, they sought to determine how the inflammation affects the skeletal muscle fibers. They injected the mice with a drug to trigger muscle inflammation, then put them on tiny treadmills to test their motor function. As expected, mice with inflammation could not keep up with the control mice, indicating reduced motor function. Examining their brain tissue, the scientists discovered the mice with muscle inflammation also had higher levels of phospho-tau.

Through additional testing, they discovered an enzyme called GSK-3 beta was responsible for increasing the tau phosphorylation. Previous studies have shown that same enzyme to cause tau buildup in the Alzheimer's brain.

Next, the scientists sought to block the accumulation of phospho-tau in the IBM mice with the goal of curbing motor function loss. In mice six months of age, one group was fed lithium chloride-laced food for six months, and a second group was fed regular food. At 12 months of age, mice in the first group performed on the treadmill as if they were six months of age, while mice in the second group had reduced motor function. Lithium chloride, the scientists found, blocked the GSK-3 beta enzyme that caused higher levels of phospho-tau.

"The older animals were performing as if they were younger animals," said Kitazawa, a postgraduate researcher of neurobiology and behavior at UCI and co-author of the study. "Lithium chloride was

delaying their rate of decline."

The scientists then sought evidence that their results in mice might translate to humans with IBM. They performed tests on human muscle tissue samples and found the GSK-3 beta enzyme again played a role in the phosphorylation of tau. That was not the case, though, in patients with other muscle disorders. "This suggests that our IBM mouse model may have the same skeletal muscle mechanism as in human cases," LaFerla said.

Source: University of California - Irvine