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A Sweet Solution to Alzheimer's Disease?

Certain variants of a simple sugar ameliorate Alzheimer's-like disease in mice, according to a new study by Canadian researchers. Although the new studies are still in the early stages, the findings could lead to new therapies that prevent or delay the onset of Alzheimer's disease.

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- Peter St George-Hyslop

The new studies show that some types of a sugar called cyclohexanehexol—also known as inositol—prevented the accumulation of amyloid β deposits, a hallmark of Alzheimer's disease. Scyllo-inositol treatment also improved cognitive abilities in the mice and allowed them to live a normal lifetime. The study appeared in advance online publication of the journal *Nature Medicine* on June 11, 2006.

HHMI international research scholar and senior author Peter St George-Hyslop cautioned that the chemicals tested in these studies are not the type of inositol sold commercially as a nutritional supplement. That type—myo-inositol—has been shown previously to be ineffective at breaking up amyloid aggregates, he said.

In the brain of a person with Alzheimer's disease, small proteins called amyloid β aggregate into plaques, and a protein called tau clumps into neurofibrillary tangles. The brain becomes inflamed and neurons atrophy and die. It's not completely clear what kind of amyloid β peptide (monomers, oligomeric aggregates, or fibrillar aggregates) is responsible for the onset of disease, said St George-Hyslop of the University of Toronto. "Because we were able to show that scyllo-inositol specifically dispersed the high-molecular-weight oligomeric aggregates, this study confirms that the initiating event is the accumulation of oligomeric aggregates of amyloid β peptide," he said.

Previous work by JoAnne McLaurin, also of the University of Toronto and lead author of the *Nature Medicine* paper, showed that several types of inositol could stop amyloid proteins from aggregating in test tubes. To see if these compounds could do the same in vivo, St George-Hyslop, McLaurin, and colleagues tested them in transgenic mice with human genes that predispose them to an Alzheimer's-like disease.

When the researchers treated these mice with scyllo-inositol, all of the animals' disease symptoms improved. Cognitive function was improved, amyloid plaques disappeared, inflammation declined, and the mice lived longer.

The scientists found that scyllo-inositol conferred these benefits not only if the mice were treated when they were very young and disease-free, but also if they were treated after the onset of disease.

As a model system, these mice “are pretty good, but they're not a perfect replica of the disease,” St George-Hyslop said. The mice do not develop tau tangles, he explained, but they are prone to amyloid plaques, brain inflammation, cognitive disturbance, and early death, just like humans with Alzheimer's disease.

The researchers found that scyllo-inositol worked better than the epi-inositol version. Scyllo-inositol produced more dramatic benefits overall, while epi-inositol worked only transiently and only when given before disease symptoms appeared.

Scyllo-inositol “is an exciting experimental therapy, but until it has actually been tested in humans, it should not be considered the cure for Alzheimer's disease,” St George-Hyslop said. “There are many things that are very

promising when done in animal models that turn out to either not work in humans or to have unexpected toxicity.”

A public Canadian company called Transition Therapeutics has regulatory approval for clinical trials of scyllo-inositol in humans with Alzheimer's disease. Phase one trials began about a week ago. St George-Hyslop has a small financial interest in the company.

St George-Hyslop and his colleagues are optimistic that scyllo-inositol will be less toxic to humans than some previous drug candidates for Alzheimer's disease. A vaccine designed to destroy amyloid β , for example, was first tested successfully in the same type of mice used in the scyllo-inositol studies, but the vaccine turned out to be toxic in some humans. It caused an autoimmune reaction in about 10 percent of patients who were immunized, St George-Hyslop said.

Autoimmune responses shouldn't be a problem with scyllo-inositol. "This compound works by a different mechanism and doesn't involve immunizing a patient with his own protein, which was probably the origin of the allergic reaction to the vaccine," the researcher said.

Another complication with previous attempts to treat Alzheimer's disease has been that some compounds—such as beta secretase inhibitors—cannot enter the brain easily, St George-Hyslop explained. Scyllo-inositol, on the other hand, readily passes through the blood-brain barrier where it is made available to the central nervous system.

Even if scyllo-inositol does prove safe and effective in humans, patients will likely still need drugs designed to attack other aspects of Alzheimer's pathology, such as tau neurofibrillary tangles, St George-Hyslop said.

“Alzheimer's disease is probably going to be treated by a cocktail of drugs,” he predicted. “Some of them might be this compound, or one like it, that blocks the toxicity and aggregation of amyloid.”