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Flies model a potential sweet treatment for Parkinson's disease

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Researchers from Tel Aviv University describe experiments that could lead to a new approach for treating Parkinson's disease (PD) using a common sweetener, mannitol. This research is presented today at the Genetics Society of America's 54th Annual *Drosophila* Research Conference in Washington D.C., April 3-7, 2013.

Mannitol is a sugar alcohol familiar as a component of sugar-free gum and candies. Originally isolated from flowering ash, mannitol is believed to have been the "manna" that rained down from the heavens in biblical times. Fungi, bacteria, algae, and plants make mannitol, but the human body can't. For most commercial uses it is extracted from seaweed although chemists can synthesize it. And it can be used for more than just a sweetener.

The Food and Drug Administration approved mannitol as an intravenous diuretic to flush out excess fluid. It also enables drugs to cross the blood-brain barrier (BBB), the tightly linked cells that form the walls of capillaries in the brain. The tight junctions holding together the cells of these tiniest blood vessels come slightly apart five minutes after an infusion of mannitol into the carotid artery, and they stay open for about 30 minutes.

Mannitol has another, less-explored talent: preventing a sticky protein called α-synuclein from gumming up the substantia nigra part of the brains of people with PD and Lewy body dementia (LBD), which has similar symptoms to PD. In the disease state, the proteins first misfold,

then form sheets that aggregate and then extend, forming gummy fibrils.

Certain biochemicals, called molecular chaperones, normally stabilize proteins and help them fold into their native three-dimensional forms, which are essential to their functions. Mannitol is a chemical chaperone. So like a delivery person who both opens the door and brings in the pizza, mannitol may be used to treat Parkinson's disease by getting into the brain and then restoring normal folding to α-synuclein.

Daniel Segal, PhD, and colleagues at Tel Aviv University investigated the effects of mannitol on the brain by feeding it to fruit flies with a form of PD that has highly aggregated α-synuclein.

The researchers used a "locomotion climbing assay" to study fly movement. Normal flies scamper right up the wall of a test tube, but flies whose brains are encumbered with α-synuclein aggregates stay at the bottom, presumably because they can't move normally. The percentage of flies that climb one centimeter in 18 seconds assesses the effect of mannitol.

An experimental run tested flies daily for 27 days. After that time, 72% of normal flies climbed up, in comparison to 38% of the PD flies. Their lack of ascension up the sides of the test tube indicated "severe motor dysfunction."

In contrast, were flies bred to harbor the human mutant α-synuclein gene, who as larvae feasted on mannitol that sweetened the medium at the bottoms of their vials. These flies fared much better—70% of them could climb after 27 days. And slices of their brains revealed a 70% decrease in accumulated misfolded protein compared to the brains of mutant flies raised on the regular medium lacking mannitol.

It's a long way from helping climbing-impaired flies to a new treatment

for people, but the research suggests a possible novel therapeutic direction. Dr. Segal, however, cautioned that people with PD or similar movement disorders should not chew a ton of mannitol-sweetened gum or sweets; that will not help their current condition. The next step for researchers is to demonstrate a rescue effect in mice, similar to improved climbing by flies, in which a rolling drum ("rotarod") activity assesses mobility.

"Until and if mannitol is proven to be efficient for PD on its own, the more conservative and possibly more immediate use can be the conventional one, using it as a BBB disruptor to facilitate entrance of other approved drugs that have problems passing through the BBB," Dr. Segal said. A preliminary clinical trial of mannitol on a small number of volunteers might follow if results in mice support those seen in the flies, he added, but that is still many research steps away.

Provided by Genetics Society of America