Rescuing fruit flies from Alzheimer's disease

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Investigators have found that fruit fly (*Drosophila melanogaster*) males -- in which the activity of an Alzheimer's disease protein is reduced by 50 percent -- show impairments in learning and memory as they age. What's more, the researchers were able to prevent the age-related deficits by treating the flies with drugs such as lithium, or by genetic manipulations that reduced nerve-cell signaling.

The research team -- Thomas A. Jongens, Ph.D., associate professor of Genetics at the University of Pennsylvania School of Medicine; Sean M. J. McBride M.D, Ph.D. and Thomas McDonald M.D., at the Albert Einstein College of Medicine; and Catherine Choi M.D., Ph.D. at Drexel University College of Medicine - worked with the familial form of Alzheimer's disease (FAD), an aggressive form of the disease that is caused by mutations in one of the two copies of the presenilin (PS) or amyloid precursor protein (APP) genes. Studies in animal models have previously shown that the FAD-linked PS mutations lead to less presenilin (psn) protein activity.

Their findings are published in this week's issue of the *Journal of Neuroscience.*

"The results from our study suggest a new route to explore for the treatment of familial Alzheimer's disease and possibly the more common sporadic forms of Alzheimer's disease," notes Jongens. "They also reveal that proper presenilin activity levels are required to maintain normal cognitive capabilities during aging."

Learning and Memory Tests in Flies

Fruit flies can hardly take a pen-and-pencil test to assess age-related memory decline. Instead, the team relied on the ability to train fruit fly males to learn and remember courtship behavior.

During courtship the male fly performs an instinctive set of behaviors to both determine if the female is receptive and to entice her to mate. The courtship activity that a male displays toward a female is affected by several factors, including the type of pheromones produced by the female, as well as her response to his courtship attempts. If the female is not receptive she releases less attractive pheromones and more aggressively discourages the male to court her. Under these conditions, the male will quickly learn to not court her as well as other females and will remember this for several hours.

The researchers found that with age, the presenilin mutant - the Alzheimer's fruit fly model -- lost the ability to learn and remember and that this age-onset cognitive deficit could be prevented by treating the flies with drugs, or by genetic manipulations that reduce metabotropic glutamate receptor (mGluR) signaling. MGluR is located on the surface of neurons, including in the hippocampus - a major memory and learning center in the brain.

In addition, treatment of older flies with these same drugs reversed the age-dependent deficits.

"A clear advantage of the drugs used in this study is that one, lithium, is currently FDA approved for other indications and the other class of drugs, the mGluR antagonists, are currently in clinical trials in humans for the treatment of Fragile X syndrome," comments Choi .

"We demonstrate that these treatments, even when begun after the onset

of cognitive impairment, can reverse memory deficits," says McBride. "This indicates that there is a window of time during which memory is impaired, but the cellular function can still be rescued with proper treatment, again allowing for the ability to form proper memory. This is a critical finding since in humans Alzheimer's is diagnosed only clinically after the onset of cognitive impairment. So, this finding may indicate that even at the point of early memory impairment, the disease may be reversible."

Relation to Fragile X Syndrome

In attempts to identify related pathways affected by a reduction in presenilin activity, the team performed genetic tests with genes known to affect cognition. They found that the presenilin mutation genetically interacts with the Fragile X mutation in fruit flies. Fragile X is the most common genetically inherited form of cognitive impairment in humans and a known cause of autism that affects about 1 in 4,000 individuals worldwide.

"We were shocked that the two genes work in what appears to be the same pathway," says Jongens. The outward characteristics of the Fragile X fly model are loss of courtship activity and memory. In earlier studies, the same research team had found that lithium and mGluR antagonists also restored normal courting behavior and memory in Fragile X flies. This is what led Jongens and his colleagues to test lithium and mGluR antagonists on the FAD-mutated fruit flies.

Eight years ago, studies outside of Penn using a mouse model proposed that Fragile X patients have a tendency to have weakened synaptic connections (sites used for neuron to neuron communication) more readily than the general population. This weakening is due to increased activity in the mGluR. In turn, this increased activity compromises neurotransmission for memory-associated functions.

These results led to the "The mGluR Theory of Fragile X," first proposed by Dr. Mark Bear at MIT and his coauthors. This theory proposed that the underlying cause of the cognitive impairment and many of the other symptoms associated with Fragile X Syndrome were due to enhanced metabotropic glutamate receptor signaling.

Jongens, McBride, and colleagues tested if mGluR overactivity might be at the root of many of phenotypes associated with their fly Fragile X model. In 2005, the team reported that treatment of fragile X flies with drugs such as lithium or mGluR antagonists restored normal courtship behavior and memory in their mutant flies and rescued some neuronal structural defects, as well. The group used lithium because it is known to have activities analogous to blocking mGluR-receptor activity, and it is already an FDA-approved drug used to treat other ailments in humans such as bipolar disorder.

A Potential Link to Calcium

Back in the Alzheimer's fly model, the team surmised that if they could rescue mutated flies with lithium or mGluR antagonists, that pathways downstream of mGluR might also be useful targets for rescuing age-related cognitive impairments. One pathway they investigated was the regulation of the inositol trisphosphate receptor (InsP3R), which releases calcium from internal stores into the cytoplasm of the cell.

They focused on this pathway because previous studies have found elevated calcium levels in the cells of Alzheimer's patients and more recently Dr. Kevin Foskett and his colleagues, also at Penn, had found that FAD mutations of presenilin make InsP3R more responsive to the signal that stimulates it to release calcium in the cytoplasm. (In normal situations, presenilin functions to cleave several transmembrane proteins, including the APP protein, which can produce the A□-peptide found in the plaques of Alzheimer's patients.)

Jongens, McBride and their colleagues found that genetic reduction of the InsP3R pathway also prevented the age-related loss of learning and memory in the FAD fly model.

"The release of calcium from internal cellular stores during the cellular encoding of memory seems to be finely tuned so that either too much or too little calcium release could impair memory formation," notes McBride.

"Our next steps will involve validating results in a relevant mouse model of FAD or AD, as well as exploring the underlying basis for this new found connection between Fragile X Syndrome and Alzheimer's disease," says Jongens. "It is intriguing that the drugs being developed for the treatment of Fragile X might also be useful in the treatment of another disease affecting cognition, namely Alzheimer's disease."

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