Restoring epigenetic balance reinstates memory in flies with Alzheimer’s disease symptoms

A fruit fly, like the kind that recovered their learning and memory capabilities as larvae in this study. Credit: Drexel University

Researchers from Drexel University reversed symptoms of Alzheimer’s disease in fruit flies by restoring the balance between two epigenetic enzymes that regulate gene expression, a study shows.

Early in the progression of Alzheimer’s disease, cognitive impairment (such as difficulties with learning and memory) may be tied to the presence of elevated levels of the HDAC2 enzyme. HDAC2 helps control how genes linked to learning and memory are expressed. It appears that when HDAC2 overwhelms

the enzyme it is paired with, which is called Tip60 HAT, it represses genes and leads to problems with neuroplasticity—the brain's ability to adapt to new stimuli or recall reactions to stimuli it already encountered.

But a research team led by Priyalakshmi Panikker, a Ph.D. student, and Felice Elefant, Ph.D., an associate professor, both in Drexel's College of Arts and Sciences, performed tests in flies and found that if they added extra Tip60 HAT in the brain of flies that displayed symptoms close to Alzheimer's disease, the balance between the enzymes could be successfully restored. When that balance came back, behaviors the team had taught the flies were able to be learned again and remembered.

"Our findings strongly support the concept of exploring the efficacy of specific Tip60 HAT activators, as well as identifying and manipulating additionally misregulated Tip60 target genes," Elefant said.

Elefant, Panikker and their team—whose findings were published in the *Journal of Neuroscience* — looked at how Alzheimer's disease affected flies early in their development, during their larval stages, to catch what might happen in Alzheimer's well before the tell-tale symptoms arise.

"Many researchers that study Alzheimer's disease utilize human post-mortem samples, and thus, they are not looking at what is happening during the early progression of neurodegeneration, including whether we can correct what is happening during these early stages ," Elefant said.

For the study, flies were taught to associate a certain odor with sucrose—table sugar, which flies eat and is a positive reinforcement. After being exposed to the scent paired with sugar, the flies learned to move towards the scent even without the sugar present.

Flies that modeled Alzheimer's disease showed no difference in their reaction to the smell they had earlier been condition

to. This showed that their ability to learn and remember this association was negatively affected.

But once Tip60 HAT was introduced in the brain to correct the identified Tip60 HAT/HDAC2 imbalance, these flies showed a reaction time comparable to the ones without the Alzheimer's type of condition. This indicated that they recovered their ability to learn and remember after the epigenetic balance was reintroduced.

Moreover, when researchers identified a collection of genes related to brain function that had been repressed in the flies—due to elevated HDAC2—an introduction of increased Tip60 HAT levels in the brain restored regular function in 9 of the 11 genes tested.

The results Panikker and Elefant found were encouraging. More testing is needed, but Elefant's goal is to find new avenues for gene therapy.

"When people age, they have a loss of memory but it's not because there are mutations in their genes," Elefant said. "It's the way they're packaged. They're distorted. And we're seeing non-invasive ways we might be able to prevent that early on."

Explore further:
Blocking enzyme linked to Alzheimer's may reverse memory loss

More information:
Priyalakshmi Panikker et al, Restoring Tip60 HAT/HDAC2 Balance in the Neurodegenerative Brain Relieves Epigenetic Transcriptional Repression and Reinstates Cognition, *The Journal of Neuroscience* (2018). DOI: 10.1523/JNEUROSCI.2840-17.2018

Journal reference:
Journal of Neuroscience