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Lipid deficiency linked to neuron degeneration

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A type of lipid that naturally declines in the aging brain impacts – within laboratory models used to study Parkinson's disease – a protein associated with the disease, according to a study co-authored by University of Alabama researchers.

The study, which published today in the *Proceedings of the National Academy of Sciences*, focuses on lipids, fat-like molecules that naturally occur in organisms, and their potential roles in a complex process that leads to the death of neurons that produce dopamine. When dopamine-producing neurons malfunction or die, this leads to the symptoms associated with Parkinson's disease.

"This gets right to the heart of understanding, possibly, the mechanism by which one form of lipid is impacting the process of neuron degeneration," said Dr. Guy Caldwell, UA professor of biological sciences and one of the study's co-authors.

The study, led by researchers at the Louisiana State University Health Sciences Center, focused on phosphatidylethanolamine, a lipid known as PE. Today's scholarly article details how low levels of PE lead to high-levels of alpha-synuclein, a protein previously linked to Parkinson's. It also show the promise a second lipid, ethanolamine, or ETA, has in boosting PE levels.

To function correctly, proteins must fold properly within cells. One misfolding, as can occur when extra copies of the protein alpha-

synuclein are present, can lead to others and, subsequently, to aggregation, or clumping, of proteins. Aggregation of proteins can lead to neuron malfunction or cell death.

Previous research had shown that excess alpha-synuclein can serve as an intra-cellular "roadblock," preventing proteins, dopamine and other things cells need from being delivered to their necessary locations. This delivery disruption can lead to serious disorders.

"That situation is being applied here, but in a different way," Caldwell said. "We're gaining a better understanding of the importance these lipids, which are components of cellular membranes, have in maintaining proper trafficking."

A proper link with alpha-synuclein helps "lipid rafts" in their transport of proteins.

"As the name implies, lipid rafts are like rafts of fat," Caldwell said. "If alpha-synuclein can't associate with those rafts, it could be a toxic situation for these cells."

Using yeast and the tiny nematode C. elegans as laboratory models, the researchers showed they could reverse the delivery problem by adding ETA to the mix.

"This supplementation of ETA basically tells us that if we can restore the amount of PE that is being made, we can create a healthier situation in neurons, and this might help them to survive longer."

UA's lead author on the study is Siyuan "Alice" Zhang, a third-year UA doctoral student who works in the Caldwell lab. Dr. Kim Caldwell, UA professor of biological sciences, is also a co-author. LSU's senior researcher on the project is Dr. Stephan Witt.

Additional study is needed in rodents and patient-derived stem cells before knowing how beneficial the discovery could eventually prove, Caldwell said.

Perhaps one day, Caldwell said, a supplement could be developed to prevent the decline of PE or possibly a drug could be developed to activate an enzyme that converts ETA to PE.

"I think it has promise as a new way of looking at alleviating toxicity," Caldwell said. "It's a different angle."

The research was supported, in part, by grants from the National Institutes of Neurological Disorders and Stroke.

This is the third article published in the *Proceedings of the National Academy of Sciences* by the Caldwell lab since March.

More information: Phosphatidylethanolamine deficiency disrupts α-synuclein homeostasis in yeast and worm models of Parkinson disease, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1411694111

Provided by University of Alabama in Tuscaloosa

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