

New Parkinson's disease drug target revealed through study of fatty acids

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Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

The human brain is rich in lipids. Investigators studying Parkinson's

disease (PD) have become increasingly interested in lipids since both molecular and genetic studies have pointed to the disruption of the balance of the brain's lipids as a potentially critical contributor to this disease. Beginning in yeast and moving through various model organisms and human cells, a new study led by investigators from Brigham and Women's Hospital and Harvard Medical School has provided insights into the role of fatty acids and suggests that inhibiting a specific enzyme can protect against neurotoxicity. Their findings, which point to a novel therapeutic approach that could be developed to treat PD and some forms of Alzheimer's disease, are published in *Molecular Cell*.

"People have been aware for many years of some connection between Parkinson's disease and the brain's lipids," said lead author Saranna Fanning, Ph.D., of the Ann Romney Center for Neurologic Diseases at the Brigham and Harvard Medical School. "Through this [collaborative effort](#), beginning with yeast models in the Lindquist lab and in the Selkoe and Dettmer labs leveraging rat cortical neurons and human [cortical neurons](#), we've identified a pathway and a therapeutic target that no one has pursued before."

Fanning's work began in the lab of the Whitehead Institute's Susan Lindquist, Ph.D., who passed away in 2016. She performed unbiased lipidomic profiling, measuring lipids and fatty acid changes in yeast that had been engineered to produce α -synuclein, a protein that forms the hallmark Lewy body clumps of PD. An increase was identified in the constituents of the neutral lipids pathway, including a monounsaturated fatty acid known as [oleic acid](#). This finding was then replicated in rodent and human neuronal models, including patient cell lines, by Fanning and colleagues in the labs of co-senior authors Dennis Selkoe, MD, and Ulf Dettmer, Ph.D., at the Brigham. Additional experiments were carried out in the roundworm *C. elegans*, another classic model organism.

"It was fascinating to see how excess α S had such consistent effects on

the neutral lipid pathway across model organisms, from simple baker's yeast and cultured rodent neurons to cells derived from PD patients that carry extra copies of α -synuclein in their genome. All our models clearly pointed at oleic acid as a mediator of α -synuclein toxicity," said Dettmer.

The team also measured signs of neurotoxicity in their models, looking for ways to target fatty acids or the pathways involved in their generation that would offer protection from PD. The researchers found that suppressing an enzyme known as stearoyl-CoA-desaturase (SCD), which helps generate oleic acid and other monounsaturated fatty acids, was protective, suggesting that SCD may be a promising therapeutic target.

While not currently used in the clinic, multiple inhibitors of SCD exist today and are used in research labs. Additional follow-up studies will be required to determine how well such testing begins in humans.

"The identification of SCD as an enzyme which contributes to α -synuclein-mediated lipid changes and neurotoxicity presents a unique opportunity for small-molecule therapies to inhibit the enzyme in models of PD and, ultimately, in human diseases," said Selkoe.

More information: Fanning, S et al. "Lipidomic Analysis of α -Synuclein Neurotoxicity Identifies Stearoyl CoA Desaturase as a Target for Parkinson Treatment" *Molecular Cell* [DOI: 10.1016/j.molcel.2018.11.028](https://doi.org/10.1016/j.molcel.2018.11.028)

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