Enzyme That Produces Fat Could Worsen Parkinson's Disease, NTU Singapore Study Reveals

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In a groundbreaking discovery that could reshape our understanding of Parkinson's disease, researchers at Nanyang Technological University, Singapore (NTU Singapore), have identified a pivotal role played by a fat-producing enzyme in exacerbating the neurodegenerative damage characteristic of this debilitating disorder. This enzyme, glycerol-3-phosphate acyltransferase (GPAT), was revealed to amplify the toxic effects of α-synuclein—a protein notorious for its harmful accumulation in Parkinson's patients—by disrupting fat metabolism within brain cells.

The collaborative team from NTU Singapore's Lee Kong Chian School of Medicine (LKCMedicine) embarked on a series of meticulous laboratory investigations to unravel the biochemical pathways through which α-synuclein inflicts cellular damage. Their experiments demonstrated that by reducing GPAT activity, they could mitigate the extent of brain cell damage, an effect confirmed in both Drosophila models and cultured mouse neurons. This novel insight positions GPAT as a crucial modulator of Parkinson's pathology, offering a promising new target for therapeutic intervention.

Mitochondria, often dubbed the cellular “power stations,” are indispensable for neuronal energy production. The researchers discovered that GPAT exacerbates the impairment of these organelles in the presence of α-synuclein toxicity, effectively delivering a synergistic “double hit” to brain cells. This mitochondrial compromise not only diminishes cellular energy generation but also potentiates neuronal vulnerability, accelerating neurodegeneration. The revelation that lipid metabolism intricately influences mitochondrial function in the context of Parkinson’s opens exciting avenues for novel treatment strategies.

According to Professor Lim Kah Leong, the lead investigator and Director of the Neuroscience & Mental Health Programme at NTU LKCMedicine, understanding the interplay between α-synuclein and cellular energy pathways is akin to a mechanic deciphering how an engine malfunctions; such comprehension is essential to innovating effective reparative therapies. As Parkinson’s disease affects over 11 million individuals worldwide and is becoming increasingly prevalent due to aging populations, innovative approaches that focus on underlying molecular mechanisms are urgently needed.

The research utilized fruit flies genetically modified to overexpress human α-synuclein, recapitulating key facets of Parkinson’s progression such as motor dysfunction and neurodegeneration. Through high-throughput genetic screening, the team identified the gene mino, encoding GPAT, as a critical facilitator of α-synuclein-induced neuronal toxicity. Reduced expression of mino attenuated neurodegenerative symptoms in the fly model, whereas its upregulation intensified disease manifestations, confirming GPAT’s central contribution.

To further explore therapeutic potential, the scientists employed FSG67, a small molecule GPAT inhibitor previously investigated in metabolic disorder contexts. Treatment with FSG67 in both fly models and mouse neuronal cultures resulted in diminished α-synuclein aggregation and associated lipid toxicity, underscoring the protective effect of targeting fat metabolism enzymes. This evidence suggests that pharmacological modulation of GPAT activity could serve as a viable approach to slowing or halting Parkinson’s progression.

Senior Research Fellow Dr. Ren Mengda emphasized that excessive lipid dysregulation magnifies α-synuclein’s neuronal harm, and that inhibiting GPAT effectively counters this exacerbation. The study’s findings illuminate a previously underappreciated connection between metabolic processes and neurodegeneration, encouraging a paradigm shift that integrates lipid biology into Parkinson’s research frameworks. Such perspectives could catalyze the development of disease-modifying agents, a critical unmet need in neurology.

Independently, Professor Tan Eng King, Deputy Chief Executive Officer and Senior Consultant in Neurology at the National Neuroscience Institute, lauded the study for its fresh insights into metabolic perturbations as drivers of brain dysfunction. He stressed the importance of expanding therapeutic horizons beyond symptomatic treatments, highlighting metabolic pathways as fertile ground for crafting innovative drugs. This research thus not only advances scientific understanding but also has profound clinical implications.

Science

The meticulous laboratory work utilized advanced genetic tools and in vivo behavioral assays to quantify neurodegenerative outcomes in fruit flies, complemented by biochemical analysis of cultured mice neurons to validate cross-species relevance. This integrative approach ensured robust findings that bridge experimental models with potential translational applications. Understanding the mechanistic basis of GPAT's role transcends pure research, edging closer to real-world impact on patient care.

Parkinson's disease pathology is complex, involving protein misfolding, mitochondrial dysfunction, and neural cell death. The discovery that lipid metabolism interfaces with these pathological axes enhances the multidimensional view necessary for effective intervention. Defining how GPAT influences α-synuclein toxicity enriches the molecular narrative and suggests that metabolic correction could ameliorate mitochondrial damage and, by extension, neuronal loss.

Looking ahead, the research team aims to deepen their investigation into GPAT inhibitors' efficacy and safety profiles, forging critical paths toward drug development. The synthesis of molecular biology, genetics, and pharmacology exemplified here sets the stage for future clinical trials. Should these inhibitors demonstrate favorable outcomes, they could inaugurate a new therapeutic class for Parkinson's, a breakthrough eagerly awaited by millions affected globally.

This pioneering study exemplifies the transformative power of integrating metabolic research within neurodegenerative disease contexts. As scientists continue to unravel the multifactorial underpinnings of Parkinson's, the role of enzymes like GPAT may serve as both biomarkers and modulators of disease severity, providing dual utility in diagnosis and treatment. The scientific community eagerly anticipates further insights that will pave the way for improved patient outcomes.

Published in the esteemed journal *Nature Communications*, this research marks a significant milestone in neuroscience, emphasizing the criticality of metabolic health within brain pathologies. It challenges traditional paradigms and opens vistas for multidisciplinary collaboration aimed at conquering Parkinson's disease. The journey from molecule to medicine holds promise, powered by discoveries such as these that bring hope to a field beset by complexity.

Health

Subject of Research:

The role of glycerol-3-phosphate acyltransferase (GPAT) enzyme in fat metabolism and its effect on α-synuclein toxicity in Parkinson's disease.

Article Title:

Fat Metabolism Enzyme GPAT Amplifies α-Synuclein Toxicity and Mitochondrial Dysfunction in Parkinson's Disease

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http://dx.doi.org/10.1038/s41467-026-68325-3

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