

Q+A

A Conversation with Kalipada Pahan, PhD:

The Role of Alpha-synuclein in the Progression of Parkinson's Disease and Other Neurodegenerative Conditions



Kalipada Pahan, PhD

Kalipada Pahan, PhD, is a professor of neurological sciences, biochemistry and pharmacology and the Floyd A. Davis, MD, Endowed Chair in Neurology at Rush University Medical Center.

Currently, he is engaged in translational biomedical research involving Parkinson's disease, dementia, Alzheimer's disease, multiple sclerosis and Batten disease.

In a recent study published in Nature Communications, Kalipada Pahan, PhD, presented his findings on the role of alpha-synuclein (α -syn) in the progression of Parkinson's disease and other neurodegenerative conditions, as well as the development of two drugs that could fundamentally alter the way patients with these diseases are treated.

The full results from Pahan's study can be found by going to <http://dx.doi.org/10.1038/s41467-021-25767-1>

Q: What is α -syn and what is its role in Parkinson's disease and other neurological disorders such as multiple system atrophy (MSA) and dementia with Lewy bodies (DLB)?

A: α -syn is a useful neuronal protein that regulates synaptic communication in the nervous system through vesicle trafficking and subsequent neurotransmitter release. Due to its pivotal function in humans, the synthesis of α -syn is tightly controlled through various multi-step biochemical pathways. Dysfunction in these biochemical pathways can result in the overproduction and misfolding of this protein. One of the pathologic hallmarks of Parkinson's disease and other neurodegenerative disorders is the presence of Lewy bodies, which contain aggregated α -syn.

Q: What are the mechanisms by which α -syn spreads and contributes to the development of neurodegenerative conditions?

A: The cause of Parkinson's disease, for instance, is not understood. However, we do know that some form of trauma, stress or lifestyle change can cause oxidative stress, neural inflammation, mitochondrial dysfunction and a breakdown in lysosomal autophagy and ubiquitin-proteasome systems. In turn, those reactions can become potential triggers of the misfolding of α -syn and its spread, which ultimately contributes to the development of diseases like Parkinson's.

Q: What was the hypothesis you were looking to evaluate in this study?

A: We hypothesized that if neuroinflammation was lowered, we should expect a reduced spread in the aggregated α -syn and the protection of dopaminergic neurons in the brain.

Q: What are the key takeaways from the study?

A: Our team found that two different peptides, the TLR2-interacting domain of Myd88 (TIDM) and NEMO-binding domain (NBD), can reduce neuroinflammation to regulate the levels of α -syn and slow its spread in the brain. Ultimately, based on our research, we believe these two peptides could potentially be used as a treatment for Parkinson's and other neurodegenerative disorders such as DLB and MSA.

The drugs, which were delivered intranasally, were found to slow inflammation, stop the spreading of α -syn and protect dopaminergic neurons in the brains of mice with Parkinson's disease. The treatments also improved the mice's gait, balance and other motor functions.

We also found that because the drugs were so specifically targeted, they did not interfere with other brain functions. In other words, no side effects were observed.

Q: What are the possible implications for patients?

A: The biggest implication is to change the way we treat Parkinson's. The current treatments are based on dopamine therapy, which helps with symptoms but doesn't address the underlying causes of Parkinson's disease. By focusing on α -syn spread, we have found a pathway toward slowing or stopping the advancement of the disease.

Another exciting possibility is the ability to administer this intervention through the nose. It's very difficult to deliver drugs across the blood-brain barrier, but our results suggest that this may be a real possibility in the future, which would obviously be great for patients.

Q: What are the next steps with this research?

A: The Innovation and Technology Transfer Office at Rush University System for Health has filed a patent application related to this discovery and has licensed the technology to a clinical-stage startup to translate this novel finding from the lab setting into the clinic.

For more information, visit rushu.rush.edu/pahan-laboratory