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Out-of-whack protein may boost Parkinson's

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A single change in a protein may play a role in whether someone develops Parkinson's disease, say University of Florida Genetics Institute researchers writing in a recent issue of the *Proceedings of the National Academy of Sciences*.

Scientists studying rats induced to display a form of Parkinson's disease discovered that a protein commonly found in brain cells can be toxic if — at one pinpoint location in its amino acid structure — it lacks a chemical compound called a phosphate.

When scientists used gene therapy to simulate a phosphate at this critical position, the rats' brain cells didn't develop the Parkinson-like pathology that would normally occur.

The finding provides new insight into the fundamentals of Parkinson's disease and the role of an abundant yet mysterious brain protein known as alpha-synuclein, which is believed to help brain cells communicate but may have a more sinister role in the development of neurological diseases.

"We have another potential target for therapy, but there is a great deal left to discover," said Nicholas Muzyczka, Ph.D., a professor of molecular genetics and microbiology in the College of Medicine and an eminent scholar with the UF Genetics Institute. "This is one more piece of information about what might be causing the toxicity in Parkinson's disease, and it gives us a little more to go on about what alpha-synuclein does in the brain."

Generally located at the synapses of nerve cells, alpha-synuclein is believed to aid in brain function, possibly by helping cells communicate with one another by controlling the release of neurotransmitters such as dopamine.

Mutations of alpha-synuclein may cause a rare, inherited form of Parkinson's, and the protein has been found to be the major component of Lewy bodies, which are abnormal clusters of protein in the brain cells of patients with Parkinson's disease.

The National Parkinson Foundation estimates 1.5 million Americans currently have Parkinson's disease and about 60,000 new cases are diagnosed each year. It is caused by the death or impairment of certain nerve cells in a part of the brain called the substantia nigra. When these cells die, the body is deprived of dopamine, a neurotransmitter vital for movement.

"We know of several enzymes that can cause phosphorylation in the proper position of the alpha-synuclein protein," said Oleg Gorbatyuk, Ph.D., an assistant professor of molecular genetics and microbiology. "Increasing their expression in brains afflicted with Parkinson's disease could possibly provide a gene therapy approach to the disease."

In experiments described in the Jan. 15 issue of PNAS, UF researchers used gene transfer to enhance the production of three versions of alpha-synuclein in the substantia nigra region on one side of the rats' brains. The other side was not treated, for comparison purposes.

Of the types of alpha-synuclein, the one that simulated phosphorylation at position 129 of the protein was nontoxic. But the other versions of the protein all caused significant loss of dopamine neurons in the substantia nigra.

“Adding a phosphate group is about the smallest thing that can possibly happen in biology,” said Mark R. Cookson, an investigator in the Cell Biology and Gene Expression Unit of the National Institute on Aging who was not involved in the research. “But this relatively minor, innocuous change can switch everything around from being a big problem to being no problem. This research really gives us an idea of some things going on in inherited cases of Parkinson’s disease, and if we use that genetic information as a handle to get into the common disease, it is possible to take this from genetics to a drug discovery program.”

Source: University of Florida