Stress takes its toll in Parkinson's disease

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We all know that living a stressful lifestyle can take its toll, making us age faster and making us more susceptible to the cold going around the office.

The same appears to be true of neurons in the brain. According to a new Northwestern Medicine study published Nov. 10 in the journal *Nature*, dopamine-releasing neurons in a region of the brain called the substantia nigra lead a lifestyle that requires lots of energy, creating stress that could lead to the neurons' premature death. Their death causes Parkinson's disease.

"Why this small group of neurons dies in Parkinson's disease is the core question we struggled with," says lead author D. James Surmeier, the Nathan Smith Davis Professor and chair of physiology at Northwestern University Feinberg School of Medicine. "Our research provides a potential answer by showing this small group of neurons uses a metabolically expensive strategy to do its job. This 'lifestyle' choice stresses the neurons' mitochondria and elevates the production of superoxide and free radicals – molecules closely linked to aging, cellular dysfunction and death."

The good news is preclinical research shows this stress can be controlled with a drug already approved for human use. By preventing calcium entry, the drug isradipine reduced the mitochondrial stress in dopamine-releasing neurons to the levels seen in neurons not affected by the disease.

Northwestern Medicine scientists currently are conducting a clinical trial to find out if isradipine can be used safely and is tolerated by patients with Parkinson's. Isradipine is already approved by the Food and Drug Administration for treatment of high blood pressure.

Parkinson's disease is the second most common neurodegenerative disease in the United States, second only to Alzheimer's disease. The average age of diagnosis is near 60. More than 1 million Americans currently have Parkinson's disease, and this number is rising as the population ages. The symptoms of Parkinson's disease include rigidity, slowness of movement and tremors. No treatment currently is known to prevent or slow the progression of Parkinson's disease.

Although most cases of Parkinson's disease have no known genetic link, Surmeier's study in mice showed that the mitochondrial stress in dopamine-releasing neurons was worsened in a genetic model of early-onset Parkinson's disease, suggesting a similar mechanism in rare familial forms of the disease and the more common forms.

Everyone loses dopamine-releasing neurons with age, Surmeier noted. "By lowering their metabolic stress level, we should be able to make dopamine-releasing neurons live longer and delay the onset of Parkinson's disease," he said. "For individuals diagnosed with Parkinson's disease, the hope is that this drug can slow disease progression, giving symptomatic therapies a broader window in which to work."

Provided by Northwestern University