Slower aging may protect cells in the brain from Parkinson's disease

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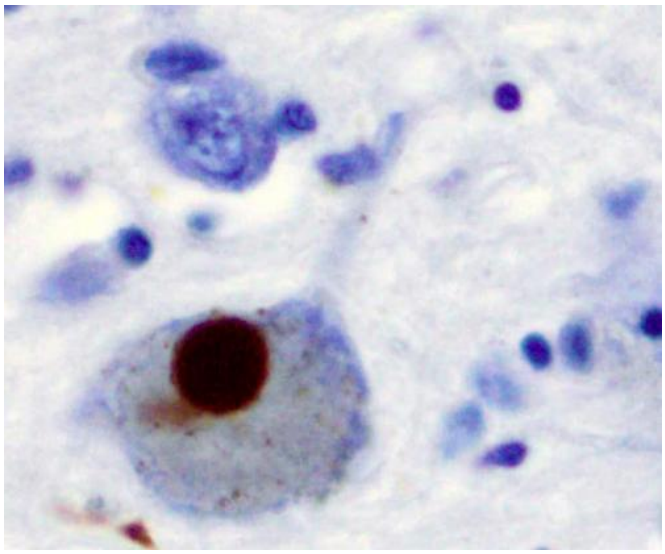

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Humans have long sought to reduce the effects of aging. Now, there may be another reason to continue searching for ways to slow the clock—preventing Parkinson's disease.

Scientists at Van Andel Research Institute (VARI) have shown in disease models that slowing aging reduces degeneration related to Parkinson's. The study was published online Nov. 19 in *npj Parkinson's Disease*, a new journal from Nature Publishing Group.

Parkinson's disease is the second most common neurodegenerative disorder and affects seven to 10 million people worldwide. Symptoms include slowed movement, resting tremor, postural instability and rigidity, as well as non-motor issues such as dementia, loss of sense of smell, sleep disturbances, constipation and depression.

"It is unknown why symptoms take many decades to develop when inherited mutations that cause the disease are present from birth," said Jeremy Van Raamsdonk, a VARI assistant professor and the study's senior author. "Aging is the greatest risk factor for developing Parkinson's—we believe changes that occur during the aging process make brain cells more susceptible to disease-causing mutations that don't cause issues in younger people."

In the brain, Parkinson's is marked by the dysfunction and death of the nerve cells that produce dopamine—a chemical that plays a key role in many important functions, including motor control. Clumps of a protein called alpha-synuclein also are found in brain cells of most people with Parkinson's, although scientists are still trying to pin down their exact role.

As part of their search for ways to prevent the disease, Van Raamsdonk's team delayed the aging process in genetic models of Parkinson's disease. They demonstrated that slower aging imparts protection against the loss of dopamine-producing cells in the brain and decreases the formation of alpha-synuclein clumps—¬both hallmark features of Parkinson's.

"This work suggests that slowing aging can have protective effects on the brain cells that otherwise may become damaged in Parkinson's," Van Raamsdonk said. "Our goal is to translate this knowledge into therapies that slow, stop or reverse disease progression."

Slowing aging, preserving brain cell function

In the study, Van Raamsdonk and his team used the worm *Caenorhabditis elegans* as a genetic model for Parkinson's. Thanks to its simple and well-mapped nervous system, and the ease of genetic manipulation and maintenance of the worm, *C. elegans* is well-suited for the identification of novel

treatment strategies for neurodegenerative diseases.

Worm models of Parkinson's disease that expressed either a mutated LRRK2 gene or a mutated alpha-synuclein gene—both of which cause Parkinson's—were crossed with a long-lived strain of the worm to create two new strains with longer lifespans.

Van Raamsdonk's team then compared the two original LRRK2 and alpha-synuclein models with normal lifespans to the resulting two long-lived Parkinson's models, and found that long-lived LRRK2 and alpha-synuclein worms lost dopamine neurons at a much slower rate than their counterparts with normal lifespans. In fact, the long-lived LRRK2 worms had more dopamine neurons left on day 30 of the study than the LRRK2 worms with a normal lifespan of three weeks had on day eight of adulthood. Slowing aging also effectively reduced motor deficits related to the loss of dopamine-producing cells and eliminated the increased sensitivity to stress shown by worms with a normal lifespan.

From worms to people

The long-lived strain of *C. elegans* Van Raamsdonk used for the crosses has a mutation in daf-2, a gene that encodes for a member of the insulin and IGF1 signaling pathways. Genes in these pathways are also associated with longevity in humans; however, therapies that affect the pathways may need to be carefully controlled to mitigate potential side effects. As such, Van Raamsdonk plans to investigate this link in other Parkinson's disease models and to search for additional pathways involved in longevity that have a lower risk of side effects, while still effectively slowing or preventing disease onset.

More information: Cooper JF, Dues DJ, Spielbauer KK, Machiela M, Senchuk MM, Van Raamsdonk JM. In press. Delaying aging is neuroprotective in Parkinson's disease: a genetic analysis in C. elegans models. NPJ Park D. www.nature.com/articles/npjparkd201522

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