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Genetic manipulation of urate alters neurodegeneration in mouse model of Parkinson's disease

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A study by Massachusetts General Hospital researchers adds further support to the possibility that increasing levels of the antioxidant urate may protect against Parkinson's disease. In their report published in *PNAS* Early Edition, the investigators report that mice with a genetic mutation increasing urate levels were protected against the kind of neurodegeneration that underlies Parkinson's disease, while the damage was worse in animals with abnormally low urate.

"These results strengthen the rationale for investigating whether elevating urate in people with Parkinson's can slow progression of the disease," says Xiqun Chen, MD, PhD, of the MassGeneral Institute for Neurodegenerative Diseases (MGH-MIND) and lead author of the *PNAS* report. "Our study is the first demonstration in an animal model that genetic elevation of urate can protect dopamine neurons from degeneration and that lowering urate can conversely exacerbate neurodegeneration."

Characterized by tremors, rigidity, difficulty walking and other symptoms, Parkinson's disease is caused by destruction of brain cells that produce the neurotransmitter dopamine. Healthy people whose urate levels are at the high end of the normal range have been found to be at reduced risk of developing Parkinson's disease. Studies led by Michael Schwarzschild, MD, PhD, director of Molecular Neurobiology Laboratory at MGH-MIND, showed that, among Parkinson's patients,

symptoms appear to progress more slowly in those with higher urate levels. These observations led Schwarzschild and his colleagues to develop the SURE-PD (Safety of URate Elevation in Parkinson's Disease) clinical trial, conducted at sites across the country through the support of the Michael J. Fox Foundation. Expected in early 2013, the results of SURE-PD will determine whether a medication that elevates urate levels should be tested further for its ability to slow the progression of disability in Parkinson's disease.

The current study by Schwarzschild's team was designed to improve understanding of how urate protects against neurodegeneration. As in most animals, mice normally have very low levels of the antioxidant because it is broken down by the enzyme urate oxidase or uricase. The higher urate levels seen in humans and great apes were caused by inactivation of the uricase gene during primate evolution. The MGH-MIND team used two strains of genetically altered mice. In one, the gene for uricase is knocked out as it is in humans, increasing urate levels in the blood and brain; in the other strain, the gene is overexpressed, reducing urate levels even lower than usual for mice. Animals from both strains were used in a standard Parkinson's modeling procedure in which a neurotoxin is injected into the dopamine-producing brain cells on one side of the brain.

As expected, the brains of animals with genetically elevated urate levels showed significantly less damage from the neurotoxin injection than did the brains of genetically normal mice. The damage was increased even more in the mice with genetically reduced urate levels, which also exhibited reduced dopamine production and worsened movement abnormalities. The researchers confirmed that genetically altering uricase expression did not affect levels of other molecules in the metabolic pathway that includes urate, supporting attribution of the protective role to urate alone.

"The biology of urate in the brain is largely unexplored," says Schwarzschild, an associate professor of Neurology at Harvard Medical School. "Understanding both urate's mechanisms of protection and the way its levels are regulated in the body will help us determine how to better harness its protective effects, if they are substantiated. We now are searching for the mediators of urate's neuroprotection and beginning to explore how it is generated and transported in different brain cells."

Provided by Massachusetts General Hospital