Potential drug lessens neurodegeneration in Parkinson's disease model

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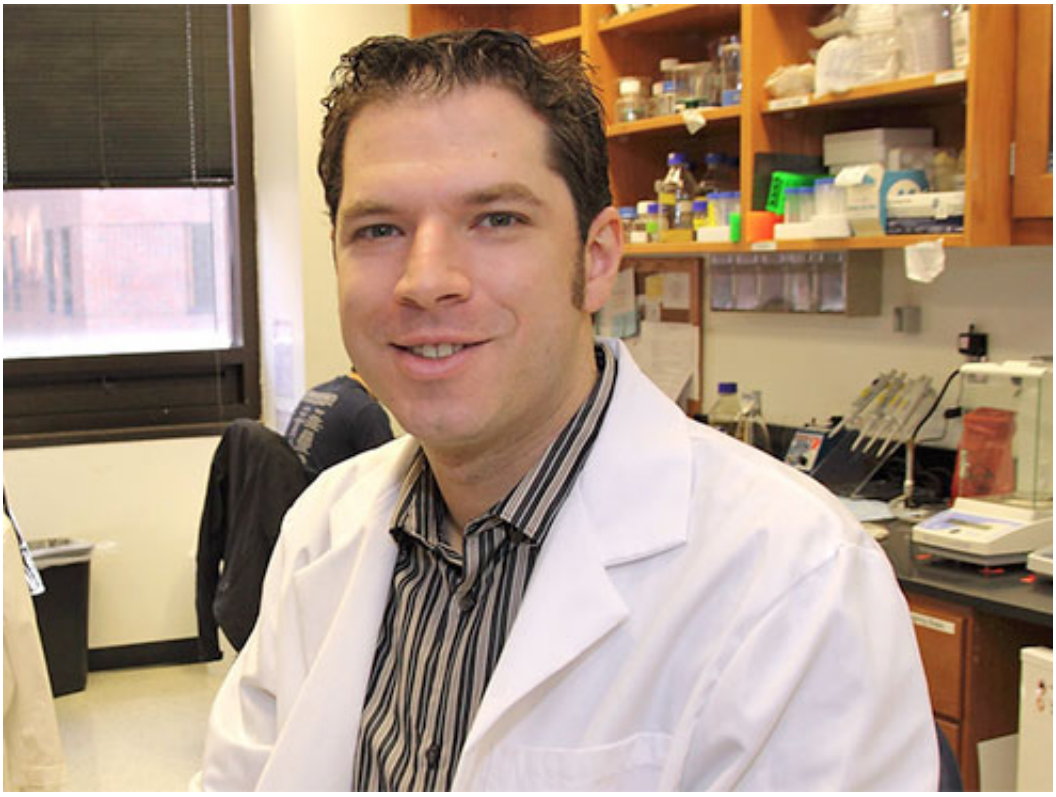

Andy West

The first test in a mammalian model of a potential new class of drugs to treat Parkinson's disease shows abatement of neurodegeneration in the brains of test rats and no significant toxicities, University of Alabama at Birmingham and Pfizer Inc. researchers report online in The *Journal of Biological Chemistry*.

At present, there are no therapies to slow or block the progression of Parkinson's disease, a common neurodegenerative disorder that affects 7 million to 10 million people worldwide.

The rat model overexpresses the protein α-synuclein in one side of the brain. This leads to degeneration of the dopamine-generating neurons of the substantia nigra region of the brain.

"Because our observations were limited to a four-week period, we are not sure whether neurodegeneration associated with α-synuclein is truly prevented or just delayed," senior author Andrew West, Ph.D., and colleagues wrote. "Either way, any interruption of neurodegeneration associated with Parkinson's disease might represent a significant therapeutic advance."

"For a patient with disease onset in the mid-60s, Parkinson's disease runs its course over 10 to 15 years," explained West, co-director of the Center for Neurodegeneration and Experimental Therapeutics, and the John A. and Ruth R. Jurenko Professor of Neurology at UAB. "So, if we can slow down the disease by even 50 percent, that may be effectively as good as a cure, given the available symptomatic treatments."

The rat model used mimics two cardinal features of Parkinson's disease: degeneration of dopamine neurons in the brain, and the accumulation of alpha-synuclein in surviving neurons. Patients with Parkinson's have significant degeneration of dopaminergic neurons in the substantia nigra, up to 70 percent losses at even mid-stages of their disease, and abnormal accumulation of α-synuclein in many of the surviving neurons that occurs years earlier. Details of how Parkinson's begins and how it progresses are still unclear.

The potential new class of drugs is kinase inhibitors that are active against the enzyme "leucine-rich repeat kinase 2" (LRRK2, pronounced

"lark two"). Two clues point to LRRK2 as a possible target for therapy in Parkinson's. First, about 2 percent of Parkinson's disease patients have a specific mutation in LRRK2 called G2019S that increases the kinase activity of LRRK2; this suggests that increased activity plays a role in progression of the disease. Second, the West lab last year reported that gene "knockout" rats with no LRRK2 are completely protected from neurodegeneration in the α-synuclein-overexpression model, suggesting pharmacological inhibition may be a viable approach.

The model uses rats that express a cloned human G2019S-LRRK2 gene. Then these rats are injected in the brain (specifically a part of the brain called the substantia nigra) with a virus that expresses human α-synuclein. Test rats were fed the test inhibitor for four weeks, beginning at the time of infection. The small-molecule inhibitor easily passes through the blood-brain barrier to reach the brain from the bloodstream. Besides protecting against neurodegeneration, the inhibitor also lessened an inflammatory response by microglial cells seen in the brain in association with G2019S-LRRK2 expression.

West and colleagues also tested the inhibitor in outbred, wild-type rats, animals that are distinct from the strain that has the human G2019S-LRRK2. With the placebo, these rats showed about a 20 percent loss of neurons after four weeks of α-synuclein overexpression; but treatment with the inhibitor completely abated that loss. This result suggests that the inhibitor also has efficacy in the absence of the human G2019S-LRRK2.

"That is important because only 2 percent of Parkinson's disease patients have the G2019S mutation," West said. "These wild-type rats really excited us because it suggests the therapeutic action of the drug may extend to the majority of Parkinson's disease patients. This has invigorated our collaborative efforts with Pfizer Inc. and the Michael J. Fox Foundation for Parkinson's Research to invest more effort in

LRRK2 inhibitors."

The Pfizer inhibitor is one of a number of LRRK2 inhibitors under development by drug companies, and also at UAB in collaboration with the Southern Research Institute. West says there will be room for several different inhibitors if this class of drugs shows promise in initial clinical trials, which hopefully will occur within the next year.

The next steps for the Pfizer inhibitor will be testing a variety of doses and testing what happens if treatment begins after the α-synuclein expression has already started. West notes that any possible therapy for Parkinson's disease will need to be incredibly safe because treatment would last for years.

"We have to be very careful with what our models can tell us," West cautioned about extrapolating from the rat model. "We need to think critically about what type of benefit we can expect to see in humans because there are recent examples where improper clinical trial design have hindered the development of a new class of drugs for years and sometimes decades."

For example, it is not clear where and how the inhibitor acts in the rat model, especially since inflammatory microglia cells in the brain also express LRRK2. Knowing such information might be critical to the success of these drugs in the clinic. In a separate trail of evidence, researchers, who include David Standaert, M.D.,Ph.D., have found that gene knockout of several neuroinflammatory processes can block α-synuclein neurodegeneration. Thus, the inhibitor may have an effect on just neurons or just microglia, or it may be a two-hit process affecting both neurons and microglia. Standaert is the John N. Whitaker Professor and chair of the Department of Neurology at UAB.

More information: "LRRK2 Pharmacological Inhibition Abates α-

Synuclein Induced Neurodegeneration." *J. Biol. Chem.* jbc.M115.660001. First Published on June 15, 2015, DOI: 10.1074/jbc.M115.660001