Parkinson's disease pathogenesis reduced in rat model by a cell-signaling inhibitor drug

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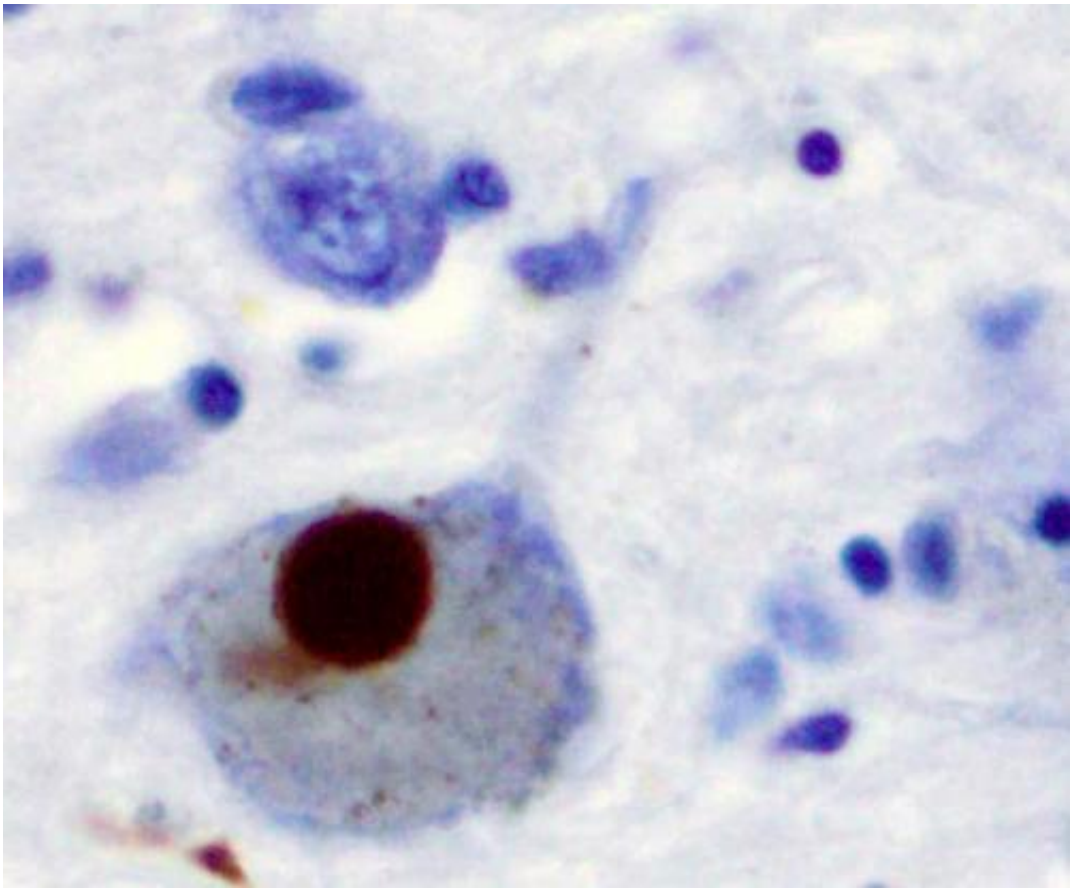

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

University of Alabama at Birmingham researchers report the first

documentation that suppressing a key cell-signaling pathway in a rat model of Parkinson's disease reduces pathogenesis. Oral administration of AZD1480—one of the JAK/STAT pathway inhibitors generally known as Jakinibs—lessened the destructive inflammation and nerve cell degradation in the area of the brain affected by Parkinson's.

At present, there are no therapies available to patients to prevent progression of Parkinson's disease, the chronic neurodegenerative movement disorder marked by profound loss of dopamine-producing neurons in the brain.

"We believe Jakinibs may become a viable therapeutic option for Parkinson's disease patients," said Etty "Tika" Benveniste, Ph.D., lead author of a paper published May 4 in *The Journal of Neuroscience*. "They are already being studied for other conditions, are orally bioavailable, seem to be well-tolerated, and do not promote troublesome immunosuppression. Furthermore, there may also be other ways of targeting the JAK/STAT pathway as a neuroprotective therapy for neurodegenerative disease."

A variety of Jakinibs are in Phase I, II or III clinical trials for several other diseases. The current UAB study, funded by the Michael J. Fox Foundation for Parkinson Research and the National Institutes of Health, is the first to show that disrupting the JAK/STAT pathway prevents the neuroinflammation and neurodegradation specific to Parkinson's disease.

"This is a very important advance," said David Standaert, M.D., Ph.D., chair of the UAB Department of Neurology and a collaborator on the project. "It shows that anti-inflammatory strategies have real potential. The next steps will be to validate some of the inflammatory changes seen in the animals in patients with Parkinson's disease, which in turn will enable planning of clinical studies of anti-inflammatory therapies in patients with Parkinson's."

Benveniste and Standaert are part of an interdisciplinary UAB team focusing on neuroinflammatory mechanisms in Parkinson's disease. The group—co-led by Benveniste, professor in the department of Cell, Developmental and Integrative Biology; Standaert, professor and chair of Neurology; and Andrew West, Ph.D., associate professor of neurology—seeks to understand how the body's immune system contributes to the pathology seen in the brains of Parkinson's disease patients and to the development and progression of the disease. Only recently have researchers begun to suspect an important role for inflammation in the disease, and this is still largely uncharted territory.

For the current paper, UAB researchers, led by Hongwei Qin, Ph.D., associate professor of cell, developmental and integrative biology, either challenged rat immune cells in vitro with aggregated human α-synuclein, or induced overexpression of α-synuclein carried by a virus vector in brains of rats. Untreated, this in vivo model leads to neuroinflammation in the brain and degradation of dopamine-producing neurons in the substantia nigra, the portion of the midbrain marked by cell death in Parkinson's patients. Accumulation of α-synuclein in the brains of patients is a core feature of Parkinson's disease, and this leads to the activation of the brain immune cells called microglia, the production of inflammatory signaling chemicals, and ultimately, neurodegradation.

In vitro and in vivo experiments showed AZD1480 inhibited JAK/STAT activation and downstream gene induction after a challenge by α-synuclein. The genes that are induced by α-synuclein, but not induced in the presence of α-synuclein and AZD1480, are associated with the proinflammatory phenotype. The inhibition by AZD1480 dampened both innate and adaptive immune responses.

Altogether, the researchers say, the results show the potential of Jakinibs to protect against the degradation of dopamine-producing neurons.

Details

For the in vivo neuroinflammation experiments, α-synuclein overexpression was induced, and two weeks later rats were given AZD1480 by oral gavage for 14 days. Then the researchers analyzed the inflammatory response in the substantia nigra of the midbrain for AZD1480-treated and -untreated animals. AZD1480 prevented the increased numbers of microglia and macrophages seen after α-synuclein overexpression. AZD1480 also prevented inflammatory activation of the microglia, as measured by Iba1-positive cells, and it prevented upregulation of genes for the proinflammatory markers TNF-α, iNOS, IL-6 and CCL2.

AZD1480 also prevented neurodegradation. For the in vivo neurodegradation experiments, α-synuclein overexpression was induced, and four weeks later—at the peak of neuroinflammation—rats were given a four-week treatment of AZD1480 oral gavage. At 12 weeks, the brains were analyzed for nigral neurons of the substantia nigra. Benveniste and colleagues found that overexpression of α-synuclein caused a 50 percent loss of nigral neurons at three months. But when the α-synuclein rats were also treated with AZD1480, that loss was prevented, and the numbers of nigral cells were similar to those of the controls.

In Parkinson's disease, chronic inflammation in the brain makes the blood-brain barrier more permeable, allowing immune system T-cells to infiltrate into the brain from the bloodstream, potentially adding to neuroinflammation. In the rat model, α-synuclein overexpression increased the infiltration of CD4+ T-helper cells and induced activation of the STAT3 signaling protein. AZD1480 treatment inhibited both of these immune responses. AZD1480 also inhibited induction of two genes for proinflammatory markers, CIITA and MHC Class II.

The UAB researchers further found that α-synuclein overexpression significantly upregulated 186 genes in the midbrains of rats, while AZD1480 treatment of α-synuclein-overexpression rats inhibited the expression levels of 59 genes, the majority being genes that were induced by α-synuclein. Genes induced by α-synuclein overexpression include many that are implicated in cell signaling, inflammatory and neurological diseases, and antigen presentation (a step in the adaptive immune response).

More information: *The Journal of Neuroscience*, DOI: 10.1523/JNEUROSCI.4658-15.2016

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