

Study identifies novel Parkinson's disease drug target

June 21 2007

Researchers at the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND) have identified a potential new drug target for the treatment of Parkinson's disease and possibly for other degenerative neurological disorders.

In an upcoming issue of the journal *Science*, the investigators describe finding, in cellular and animal models, that blocking the action of an enzyme called SIRT2 can protect the neurons damaged in Parkinson's disease from the toxic effects of alpha-synuclein, a protein that accumulates in the brains of Parkinson's patients. The study, which also suggests that inhibiting this pathway could help in the treatment of other conditions in which abnormal proteins accumulate in the brain, is receiving early online release on the *Science Express* website.

"We have discovered a compelling new therapeutic approach for Parkinson's disease, which we expect will allow our scientists – as well as those at pharmaceutical and biotech companies – to pursue innovative new drugs that will treat and perhaps even cure this disorder," says Aleksey Kazantsev, PhD, director of MGH-MIND Drug Discovery Laboratory, who led the *Science* study. "Since the same sort of aggregation of misfolded proteins has been reported in Huntington's and Alzheimer's diseases - as well as Lewy body dementia, which also involves alpha-synuclein deposits - we plan to test this approach in those conditions as well."

Parkinson's disease – characterized by tremors, rigidity, difficulty walking and other symptoms – is caused by the destruction of brain cells that produce the neurotransmitter dopamine. In recent years researchers at several centers have been studying the role of alpha-synuclein accumulations in dopamine-producing neurons, observed in patients with both inherited and sporadic Parkinson's disease. MGH-MIND investigators have discovered that, in Parkinson's, the alpha-synuclein molecule folds abnormally and form aggregates called inclusion bodies. Such inclusions of other abnormal proteins are seen in several disorders, but whether inclusions are toxic or protective to neurons has been controversial.

In a paper published last year in the Proceedings of the National Academy of Sciences, a research team led by Kazantsev analyzed ways to reduce the size of inclusions containing misfolded versions of alpha-synuclein or of the Huntington's disease-associated protein huntingtin. They found that a compound called B2, which promotes the formation of larger inclusions, paradoxically appeared to reduce toxicity in cellular disease models, possibly by reducing the overall number of inclusions.

In the current study, the investigators began by seeking the mechanism underlying the observed effects of B2. Assays of the compound's activity against a panel of key enzymes identified only one significant association – a weak but selective inhibition of SIRT2, which is known to regulate the cell cycle and may have a role in aging. An experiment using RNA interference to suppress SIRT2 and a related enzyme in human cell lines expressing alpha-synuclein confirmed that only the inhibition of SIRT2 reduced alpha-synuclein toxicity.

Kazantsev's team then developed and identified more powerful inhibitors of SIRT2, based on the structure of B2. One of these novel inhibitors called AGK2 had 10 times the potency of B2 and was shown to protect dopamine-producing neurons from alpha-synuclein toxicity in

cultured rat neurons and in an insect model of PD. Several additional compounds that act on the SIRT2 pathway have been identified, some which may be even better than AGK2 as candidates for drug development.

SIRT2 is known to act on a major protein component of microtubules, cellular structures that help move objects within cells, among other functions. The researchers theorize that inhibiting SIRT2 might promote microtubule-dependent transportation of alpha-synuclein into large aggregates; or it could strengthen microtubules that have been destabilized by misfolded alpha-synuclein.

Kazantsev explains, “For Parkinson’s disease, we can now pursue a straightforward drug development process by identifying potent and selective candidates from this class of compounds that can be tested in animal studies and eventual human trials. One of the most satisfying aspects is how this discovery validates our approach to drug discovery, which incorporates both the most advanced tools for screening candidate compounds and outstanding collaboration with our clinical and scientific experts in human disease.” Kazantsev is an assistant professor of Neurology at Harvard Medical School.

Source: Massachusetts General Hospital

Citation: Study identifies novel Parkinson's disease drug target (2007, June 21) retrieved 26 April 2024 from <https://medicalxpress.com/news/2007-06-parkinson-disease-drug.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.