Enzyme inhibition protects against Huntington's disease damage in two animal models

29 November 2012

Treatment with a novel agent that inhibits the activity of SIRT2, an enzyme that regulates many important cellular functions, reduced neurological damage, slowed the loss of motor function and extended survival in two animal models of Huntington's disease. The study led by Massachusetts General Hospital (MGH) researchers will appear in the Dec. 27 issue of *Cell Reports* and is receiving advance online release.

"I believe that the drug efficacy demonstrated in two distinct genetic HD mouse models is quite unique and highly encouraging," says Aleksey Kazantsev, PhD, of the MassGeneral Institute for Neurodegenerative Disorders, senior author of the study. "The outcome suggests that designing stronger SIRT2 inhibitors is a valid strategy for developing drugs to slow the progression of HD, something that currently does not exist."

Earlier studies by Kazantsev's group and others showed that inhibiting SIRT2 (sirtuin-2 deacetylase) protected against neuronal damage in cellular and animal models of HD and Parkinson's disease – both of which are characterized by the buildup of abnormal proteins in the brain – and in other neurodegenerative disorders. The current study was designed to evaluate in two mouse models of HD use of a new, brain-permeable SIRT2 inhibitor called AK-7, first identified by members of the MGH team in 2011. One model called R6/2 is characterized by robust progression and severity of neurological symptoms. The other, called 140 CAG Htt knock-in, is genetically closer to the human disease. In both models, the mutated huntingtin gene contains extended repeats of the nucleotide triplet CAG, leading to development of HD-like motor symptoms and the same type of brain damage seen in the devastating neurological disorder.

Animals from both strains received two daily injections of AK-7 at one of three dose levels – 10, 20 or 30 mg/kg – beginning at the age of 4 weeks and continuing for up to 14 weeks. Among the R6/2 animals, those treated with AK-7 retained significantly more motor function than did untreated animals and had less shrinkage of brain structures affected by HD and smaller aggregates of the mutant huntingtin protein characteristic of the disorder. Treated animals in this model, which usually die prematurely, lived 13 percent longer than untreated R6/2 mice.

In the experiments with the 140 CAG Htt knock-in model, treated animals maintained activity levels similar to those of normal mice for several months, while untreated mice showed a rapid decline in motor activity. In that model, 14 weeks of treatment reduced mutant huntingtin aggregates in the most affected area of the brain by more than 50 percent, compared with untreated animals from the same strain.

"The golden rule in the HD field for identifying compounds that could work in patients is showing efficacy in a robust HD model like R6/2 and in the more genetically accurate to human disease 140 CAG Htt knock-in model," says Kazantsev, an associate professor of Neurology at Harvard Medical School. "The next essential and critical step will be testing additional, structurally diverse SIRT2 inhibitors in HD mice, and we are preparing to test one that is 10 times more potent than AK-7. If and when that compound and others also show efficacy, that will give us definitive proof of the therapeutic potential of SIRT2 inhibition for HD."

Provided by Massachusetts General Hospital