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Small changes in protein chemistry play large role in Huntington's disease

In Huntington's disease, a mutated protein in the body becomes toxic to brain cells. Recent studies have demonstrated that a small region adjacent to the mutated segment plays a major role in the toxicity. Two new studies supported by the National Institutes of Health show that very slight changes to this region can eliminate signs of Huntington's disease in mice.

Researchers do not fully understand why the protein (called mutant huntingtin) is toxic, but one clue is that it accumulates in ordered clumps of fibrils, perhaps clogging up the cells' internal machinery.

"These studies shed light on the structure and biochemistry of the mutant huntingtin protein and on potentially modifiable factors that affect its toxicity," said Margaret Sutherland, Ph.D., a program director at NIH's National Institute of Neurological Disorders and Stroke (NINDS). "They reveal sites within the huntingtin protein and within broader disease pathways that could serve as targets for drug therapy."

Both studies were published online this week. One study, published in the *Journal of Cell Biology*, was led by Leslie Thompson, Ph.D., and Joan Steffan, Ph.D., of the University of California, Irvine. The other study, in *Neuron*, was led by X. William Yang, M.D., Ph.D., of the University of California, Los Angeles in collaboration with Ron Wetzal, Ph.D., of the University of Pittsburgh School of Medicine.

Huntington's disease is inherited, and usually strikes in middle age, producing uncontrollable movements of the legs and arms, a loss of muscle coordination, and changes in personality and intellect. It is inexorably progressive and leads to death of affected persons usually within 20 years after symptoms first appear. Individuals with the disease carry mutations that affect the huntingtin protein. The mutations involve a triple repeat DNA sequence, a type of genetic miscue similarly found in Friedreich's ataxia, Kennedy's disease, fragile X syndrome, and other neurodegenerative disorders.

The normal huntingtin protein consists of about 3,150 amino acids (which are the building blocks for all proteins). In individuals with Huntington's disease, the mutated protein contains an abnormally long string of a single amino acid repeat; lengthier chains are associated with worse symptoms and earlier onset of the disease. In recent years, however, researchers have begun looking at the effects of other, nearby amino acids in this large protein – and in particular, biochemical changes to those amino acids.

In their study, Drs. Steffan and Thompson investigated how a process called phosphorylation affects huntingtin. Phosphorylation is the attachment of chemical tags, known as phosphates, onto the amino acids in a protein. The process occurs naturally and is a way of marking proteins for destruction by cellular waste handling systems. The researchers liken it to putting a sign on a pile of junk that tells the garbage collectors to take it away. Their study shows that phosphorylation of just two amino acids, located at one end of huntingtin, targets the protein for destruction and protects against the toxic effects of the mutant protein.

"Clearance of mutant huntingtin is likely regulated at many levels, but our data establish that these two amino acids are critical," Dr. Steffan said.

Could boosting phosphorylation of those two amino acids reduce the buildup of huntingtin and improve symptoms of the disease? In parallel with the UC Irvine research, Dr. Yang and his team at UCLA were asking that question using an animal model of Huntington's disease. Previously, Dr. Yang had created mice that carry the mutant huntingtin gene. These mice develop symptoms reminiscent of Huntington's disease in humans, including poor coordination, mental changes such as increased anxiety, loss of brain tissue, and accumulation of clumps of huntingtin in brain cells.

Through further genetic engineering, Dr. Yang altered the same two critical amino acids at the end of the mutant huntingtin protein to either mimic phosphorylation (phosphomimetic) or resist it (phosphoresistant). Mice with the phosphoresistant version of the protein developed symptoms of Huntington's, but mice with the phosphomimetic version remained free of symptoms and huntingtin clumps up to one year.

Meanwhile, test tube experiments by Dr. Wetzel's group in Pittsburgh showed that phosphomimetic modification of a huntingtin fragment reduced its tendency to form clumps. Together, data from the mouse and test tube experiments provide strong support for the idea that phosphorylation acts as a molecular switch to alter clumping of the mutant protein, the researchers said.

The nearly complete lack of any signs of disease in the phosphomimetic Huntington mice may point toward new strategies to treat the disorder someday. Dr. Yang said, "Drugs that enhance or mimic the effects of phosphorylation may help to detoxify the mutant huntingtin protein."

If such drugs could be developed, Drs. Steffan and Thompson theorize, they would likely be most effective at early stages of the disease, but less so at later stages, when the clearance machinery appears to run down. Dr. Yang said he plans to examine older mice carrying the phosphomimetic version of mutant huntingtin to determine how long they are protected from the disease.

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Co-authors of the *Journal of Cell Biology* study included J. Lawrence Marsh, Ph.D. and Lan Huang, Ph.D., at UC Irvine; Ana Maria Cuervo, M.D., Ph.D., at Albert Einstein College of Medicine, New York City; Donald C. Lo, Ph.D. at Duke University, Durham, N.C.; Paul H. Patterson, Ph.D., at California Institute of Technology, Pasadena; and Steven Finkbeiner, M.D., Ph.D., at the University of California, San Francisco.

Co-authors of the *Neuron* study included Xiaofeng Gu, M.D., Ph.D., and Erin Greiner at UCLA; Rakesh Mishra and Ravindra Kodali, Ph.D., at the University of Pittsburgh; Alex Osmand, Ph.D., at the University of Tennessee, Knoxville; and Dr. Finkbeiner at UCSF.

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For more information about Huntington's disease, visit <http://www.ninds.nih.gov/disorders/huntington/huntington.htm>.

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