Animal study points to a treatment for Huntington's disease

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Beverly L. Davidson, Ph.D., a gene therapy expert, is the director of The Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia. Credit: The Children's Hospital of Philadelphia

By adjusting the levels of a key signaling protein, researchers improved motor function and brain abnormalities in experimental animals with a

form of Huntington's disease, a severe neurodegenerative disorder. The new findings may lay the groundwork of a novel treatment for people with this fatal, progressive disease.

"This research shows the intricate workings of a biological pathway crucial to the development of Huntington's disease, and is highly relevant to drug development," said study leader Beverly L. Davidson, Ph.D., director of The Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia (CHOP). "Our results in animals open the door to a promising potential therapy, based on carefully manipulating the dysregulated pathway to treat this devastating human disease."

She added that restoring proper balance to these delicate biological processes may offer even broader benefits in treating other neurological diseases, such as amyotrophic lateral sclerosis (ALS), fragile X mental retardation and autism.

The study team published its results online Dec. 31 in the journal *Neuron*.

Huntington's disease is an incurable, inherited disease entailing progressive loss of brain cells and motor function, usually beginning in midlife. A defective gene produces repeated copies of a protein called huntingtin, or HTT. The mutant HTT protein (mHTT) particularly damages a brain region called the striatum, where it interferes with normal cell growth and other fundamental biological events. The resulting disease includes involuntary movements and severe cognitive and emotional disturbances. About 30,000 Americans have Huntington's disease (HD).

Neuroscientists already knew that a signaling protein called mTORC1 that regulates cell growth and metabolism plays a major role in HD.

Many researchers have proposed that inhibiting or shutting off the mTORC1 pathway, which interacts with the deleterious mHTT proteins, could help treat HD.

The current study contradicts those assumptions. "We show that the mTORC1 pathway is already impaired in Huntington's disease, and that improving how the pathway functions actually has a protective effect," said Davidson. "However, restoring that pathway must be done very carefully to avoid further harm. It's a 'Goldilocks effect.' You need to restore the mTORC1 level; either too much or too little is detrimental."

In mice bred to model features of Huntington's disease, the study team injected bioengineered viruses as a gene therapy tool to carry DNA that directed the production of regulatory proteins called Rheb and Rhes. Both proteins act along the mTORC1 pathway. The treated mice had improvements in brain volume and in their movements. The mice had improved metabolic functions as well, such as cholesterol levels, dopamine signaling and mitochondrial activity (an indicator of cellular energy production). There also were increases in autophagy, an organism's cleanup process that clears out and recycles mHTT and other proteins.

"It was particularly exciting to see plasticity in the neurons impaired by mHTT," said Davidson, noting that in the HD mice, brain areas that had begun to atrophy recovered volume and permitted better motor function after the researchers restored mTORC1 activity to more normal levels. "This shows that brain cells are capable of responding even after disease onset, and hints at the potential for reversing Huntington's disease."

The study team performed much of this research in Davidson's laboratory at the University of Iowa, before she and many of her colleagues moved to CHOP in 2014. John H. Lee, the paper's first author, remains at the University of Iowa, where he is completing his

M.D./Ph.D. training.

Much work remains to translate these scientific findings into a clinical treatment. Researchers must identify drug candidates that appropriately activate the mTORC1 pathway. Although gene therapy vectors delivered to brain were used for this research, Davidson envisions developing a small molecule that can appropriately modulate this pathway. Such a treatment might be combined with a gene therapy approach, also being pursued by her team and other groups, delivered directly to the brain to curtail mHTT expression.

More broadly, she added, restoring mTORC1 activity to normal levels may benefit patients with other neurological diseases. Fragile X mental retardation and autism both feature overactive mTORC1 activity, while mTORC1 is reduced in ALS and HD. "This pathway is poised on a biological teeter-totter," she concluded, "and our work highlights that it's essential to control its activity to find the appropriate balance for each disease."

More information: "Reinstating aberrant mTORC1 activity in Huntington's disease mice improves disease phenotypes," *Neuron*, published online Dec. 31, 2014; to appear in print Jan. 21, 2015. doi.org/10.1016/j.neuron.2014.12.019

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