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Increase in Transcription Co-activator May Help Combat Huntington's Disease

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NEW YORK (Reuters Health) - Increasing the expression of PPAR-gamma co-activator 1 alpha (PGC-1-alpha), a key transcription regulator of mitochondrial function, can reduce the neuronal dysfunction and neurodegeneration seen with Huntington's disease (HD), the results of an animal study suggest.

"This study continues a story that we and others published in 2006, when we showed that the nuclear transcription abnormality in HD and the mitochondrial dysfunction in HD share a common pathway -- i.e. interference with the function of the transcription co-activator PGC-1-alpha," senior author Dr. Albert La Spada told Reuters Health.

According to Dr. La Spada, a researcher with the University of Washington, Seattle, the discovery of PGC-1-alpha as an important player in HD actually came from studying the non-neurologic signs and symptoms in a murine model of the disease. An analysis of the findings revealed that the molecular pathology was also relevant for the neurodegeneration seen.

"The current study," he explained, "follows up on (the earlier) work, as we test the hypothesis that genetic upregulation of PGC-1-alpha in a HD mouse model will ameliorate the disease." The findings were presented Wednesday at the American Society of Human Genetics annual meeting in Philadelphia.

The team crossed HD mice with other mice in which PGC-1-alpha was inducible by doxycycline treatment. The results indicate that PGC-1-alpha upregulation does, in fact, improve HD, although the impact on pathologic brain findings was unexpected.

"The surprising finding is that PGC-1-alpha upregulation dramatically reduces the amount of protein aggregates in the brains of the HD transgenic mice," Dr. La Spada said. "The effect is so pronounced that it raises crucial questions about how PGC-1-alpha is doing this. This is an entirely novel line of investigation that takes the work in a new direction."

Further research is needed to determine how PGC-1-alpha induces the turnover of mutant huntingtin protein and stops protein aggregation, he said. This could have important implications for addressing the toxic misfolded proteins seen with a variety of neurologic disorders, including Alzheimer's disease, Parkinson's disease, and prion diseases.