Huntington's disease protein has broader effects on brain, study shows

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In Huntington's disease, the mutant protein known as huntingtin leads to the degeneration of a part of the brain known as the basal ganglia, causing the motor disturbances that represent one of the most defining features of the fatal disease. But a new study reported in the April issue of *Cell Metabolism*, a Cell Press publication, shows that the mutant protein also is responsible for metabolic imbalances in the hypothalamus, a brain region that plays an important role in appetite control.

"This helps to explain metabolic changes and increases in appetite that have been observed in people at the early stages of disease," even before any motor symptoms appear, said Åsa Petersén of Lund University in Sweden. "It should encourage us to do more clinical studies. If we really understand the pathways that are affected, it may lead to new targets for intervention."

The clinical diagnosis of Huntington's disease is based entirely on the presence of overt motor dysfunction. But, in fact, Petersén said, the original publication that defined the disease back in 1872 described a wide spectrum of problems: motor abnormalities, depression, cognitive decline and changes in body weight among them. Subsequent studies of the Huntington's brain traced the motor disturbances to massive losses of the basal ganglia. "Those findings overshadowed other changes," Petersén said.

But Petersén spends half of her time working as a clinician. She sees

people with a diagnosis of Huntington's disease and carriers of the disease – people who know they carry the mutant gene and are therefore guaranteed to get the disease but who don't yet have any motor symptoms at all. "They complain about other symptoms," she said, including depression, anxiety, sleep disturbances and increases in appetite and weight.

Those anecdotes led her to suspect that the mutant protein, which is ubiquitously expressed, might have effects on other parts of the brain, and the hypothalamus in particular. In an earlier study, she examined the brains of Huntington's carriers to find structural changes in the hypothalamus that could be observed 10 years before motor symptoms set in, along with shifts in brain chemistry.

In the new study, Petersén and her colleagues set out to confirm that those metabolic abnormalities are due to the effects of mutant huntingtin. First they showed that mice with Huntington's disease develop impaired glucose metabolism along with pronounced resistance to insulin and the fat hormone leptin. Those metabolic symptoms could be reproduced in mice that only expressed the mutant huntingtin in the hypothalamus. When the researchers disabled the mutant huntingtin protein only in the hypothalamus, those metabolic disturbances disappeared.

"Our findings establish a causal link between mutant huntingtin expression in the hypothalamus and metabolic dysfunction," the researchers wrote. They also suggest that metabolic parameters could serve as powerful readouts for assessing therapies aimed at treating the disease by targeting the mutant protein in the brain.

Petersén says she suspects the mutant huntingtin will ultimately be found to influence other processes, both in the brain and in other tissues. She has plans to further explore the connection between the mutant protein

and the depression, anxiety and other symptoms that also may be early signs of the disease.

In the broader scheme of things, she says the new findings highlight the important links between the study of metabolism and neuroscience. "There's a lot to be gained through cross-fertilization between the two fields," she said.

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