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Study Finds Many Causes of Huntington's Neuron Death

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By Anne Harding

NEW YORK (Reuters Health) Jul 30 - The brain damage that occurs in Huntington's disease appears to be a compound injury caused by several different molecular abnormalities, a new report demonstrates.

And while these abnormalities are seen throughout the brain and even in skin cells, they only kill cells in certain vulnerable parts of the brain, suggesting cells elsewhere in the brain and body are able to cope with the abnormalities, Dr. Ole Isacson of Harvard Medical School in Boston and colleagues found.

The findings were reported in the July 21st online edition of the *Annals of Neurology*.

Huntington's disease is caused by expanded CAG repeats in the huntingtin gene, which produces an abnormal form of the huntingtin protein. Aggregations of the mutant protein collect outside neurons, the researchers note, and defects in a mechanism for "cleaning up" abnormal proteins, the ubiquitin proteasome system (UPS), have been proposed to play a role in the pathology of Huntington's disease, as well as other neurodegenerative diseases, such as Parkinson's and Alzheimer's disease.

Studies have also found that normal huntingtin upregulates production of brain-derived neurotrophic factor (BDNF), while the mutated gene does not. Mitochondrial enzyme complex II/III (MCII) dysfunction has also been proposed to be part of the pathological process in Huntington's. But the precise factors leading to the destruction of neurons within the corpus striatum in Huntington's disease patients are not yet clear.

To investigate these mechanisms, Dr. Isacson, lead author Dr. Hyemyung Seo and colleagues studied postmortem brain samples from 17 Huntington's disease patients and 6 normal controls. Half of each brain had been fresh frozen, allowing the researchers to perform biochemistry experiments as well as pathology studies.

The researchers found decreased UPS function throughout the brains of patients with both early and late stage Huntington's, as well as in samples of skin fibroblasts from people with the disease. But total levels of ubiquitin, which "tags" abnormal proteins for their removal, were high only in the vulnerable regions of the Huntington's patients' brains.

Reduced BDNF levels were seen in Huntington's patients' brains, including those of patients with early disease who had little or no microscopic pathology. The abnormalities were seen in the cortex, cerebellum and substantia nigra, as well as the striatum. Impaired MCII function also was seen in all of the Huntington's brains, but only in the striatum.

The destruction of vulnerable neurons is thus caused by several mechanisms, none of which on their own would be enough to kill the cells, the researchers conclude.

The findings suggest that therapies aimed at preventing or treating Huntington's disease will need to attack a number of targets, but also offer the hope of learning from how cells that are affected by these abnormalities but not impaired manage to cope with them, Dr. Isacson told Reuters Health.

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"In the future we will either learn from the coping mechanisms of the cells that survive and try to teach the cells that don't survive how to do that by giving them drugs or new genetic material, or we will learn how to eliminate the abnormal gene expression in the most vulnerable regions," he said.

In an editorial accompanying the report, Dr. Mark Cookson of the National Institute of Aging in Bethesda, Maryland, notes that a similarly complex series of events are probably at play in other types of neurodegenerative diseases involving proteasome dysfunction.

Ann Neurol 2004.
