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Brain degeneration in Huntington's disease caused by amino acid deficiency

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Working with genetically engineered mice, Johns Hopkins neuroscientists report they have identified what they believe is the cause of the vast disintegration of a part of the brain called the corpus striatum in rodents and people with Huntington's disease: loss of the ability to make the amino acid cysteine. They also found that disease progression slowed in mice that were fed a diet rich in cysteine, which is found in foods such as wheat germ and whey protein.

Their results suggest further investigation into cysteine supplementation as a candidate therapeutic in people with the disease.

Up to 90 percent of the human corpus striatum, a brain structure that moderates mood, movement and cognition, degenerates in people with Huntington's disease, a condition marked by widespread motor and intellectual disability. And while the genetic mutation underlying Huntington's disease has long been known, the precise cause of that degeneration has remained a mystery.

In a report on their discovery in the advanced online publication of *Nature* on March 26, the Johns Hopkins researchers, led by Solomon Snyder, M.D., tracked the degenerative process to the absence of an enzyme, cystathionine gamma lyase, or CSE.

"Usually it's very hard, if not impossible, to develop straightforward mechanisms that explain what's going on in a disease. What's even harder is even if you can find a mechanism that causes a tissue to rot,

usually there's nothing you can do about it," says Snyder, a professor of neuroscience at the Johns Hopkins University School of Medicine. "In this case, there is."

Huntington's disease, an inherited disorder, does its damage because of abnormal DNA coding for the amino acid glutamine. Healthy individuals have some 15 to 20 DNA "repeats" in that part of their genetic code, while Huntington's disease gene carriers have more than 36—and often upward of 100. Children born to a parent carrier have a 50/50 chance of inheriting the disorder, and the greater the number of repeats, the earlier the age of onset of the incurable disorder.

Bindu Diana Paul, Ph.D., a molecular neuroscientist and faculty instructor in Snyder's laboratory, was studying mice lacking CSE, which helps make the amino acid cysteine and hydrogen sulfide that moderate blood pressure and heart function. Paul, who had previous research experience with Huntington's disease, says she was startled to observe that her mutant mice also behaved a lot like those with the disease.

When a normal mouse is dangled upside down from its tail, it will twist and turn and try to bite the offending hand, she explains. But her CSE-knockout mice stayed relatively still and clasped their paws together—the same behavior she'd observed in mice with the rodent equivalent of Huntington's disease. "It looked like there was a neurological deficit," Paul says. "But nobody had looked at CSE in the brain."

Paul and Snyder began monitoring CSE in mouse and human brain tissues and found considerably less CSE in all diseased tissues. All people carry some normal huntingtin protein made by the Huntington's disease gene, although the protein's function remains elusive. But people with Huntington's disease also carry mutant huntingtin proteins. Snyder and his team saw that the mutant proteins were attaching themselves to a

crucial protein responsible for turning the CSE gene on or off, which ultimately led the diseased rodent and human brain tissues to be deprived of cysteine.

To see if loss of cysteine was directly responsible for the symptoms associated with Huntington's disease, the Johns Hopkins team turned to readily available sources of the substance in everyday foods and fed mice a cysteine-rich diet.

The results, Paul says, were striking. When those mice were dangled from their tails, they resumed struggling, although with a bit less vigor than their healthy peers. They were able to grip an object with greater strength, and they took longer to fall off a balancing apparatus than CSE-knockout mice. Their life expectancies increased one to two weeks.

Snyder and Paul say they are cautiously optimistic about the results, noting that although they suggest a possible treatment for Huntington's disease, it's clear that a high cysteine diet merely slows rather than halts the progression of the disease. Moreover, the results in live mice may not occur in humans.

More information: Paper: dx.doi.org/10.1038/nature13136

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