Mystery solved: Tiny protein-activator responsible for brain cell damage in Huntington disease

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Johns Hopkins brain scientists have figured out why a faulty protein accumulates in cells everywhere in the bodies of people with Huntington's disease (HD), but only kills cells in the part of the brain that controls movement, causing negligible damage to tissues elsewhere. The answer, reported this week in *Science*, lies in one tiny protein called "Rhes" that's found only in the part of the brain that controls movement. The findings, according to the Hopkins scientists, explain the unique pattern of brain damage in HD and its symptoms, as well as offer a strategy for new therapy.

HD itself is caused by a genetic defect that produces a mutant version of the protein "huntingtin" that gathers in all cells of the body, but only seems to affect the brain. Passed from parent to child through an alteration of a normal gene, HD over time causes irreversible uncontrolled movement, loss of intellectual function, emotional disturbances and death.

"It's always been a mystery why, if the protein made by the HD gene is seen in all cells of the body, only the brain, and only a particular part of the brain, the corpus striatum, deteriorates," says Solomon H. Snyder, M.D., professor of neuroscience at Johns Hopkins. "By finding the basic culprit, the potential is there to develop drugs that target it and either prevent symptoms or slow them down."

Curious about the huntingtin protein's striatal-specific effect, Snyder's research team, led by Srinivasa Subramaniam, Ph.D., a postdoctoral fellow, searched for proteins that interacted locally, specifically and exclusively with huntingtin in the corpus striatum, guessing that the molecular answer to the mystery most likely would be found there.

The protein Rhes caught their attention because they already were studying a related protein for other reasons. Rhes was known to be found almost exclusively in the corpus striatum.

Conducting tests using human and mouse cells, they found that Rhes interacted with both healthy and mutant versions of huntingtin protein, but bound much more strongly to mutant huntingtin, also known as mHtt.

"Touching or binding is one matter, but death is altogether another," said Snyder, so the next step was to see whether and how Rhes plus mHtt could kill brain cells in the corpus striatum.

Using human embryonic cells and brain cells taken from mice the researchers added different combinations of normal and mutant huntingtin and Rhes, and examined the cells over the next week to see if any cells died.

While each protein alone didn't change the number of cells in the dishes, when both mHtt and Rhes were present in the same cells, half the cells died within 48 hours.

"Here's the Rhes protein, we've known about it for years, nobody ever really knew what it did in the brain or anywhere else," says Snyder. "And it turns out it looks like the key to Huntington's disease."

Snyder's team then went on to tackle another mystery surrounding the

disease, the solution to this one adding further evidence for the role Rhes plays in HD.

"We've known for a long time that abnormal huntingtin proteins aggregate and form clumps in all cells of the body, but the corpus striatum of HD patients seems to have fewer of these clumps than other brain regions or the rest of the body," says Subramaniam in describing the mystery. "This has led to much controversy: Are the clumps toxic, or is it the lack of clumps that's toxic to these brain cells?"

In their experiment, adding Rhes to cells with abnormal huntingtin led to fewer clumps, but the cells died. The results, says Subramaniam, suggest that Rhes might be responsible for unclumping mutant huntingtin protein and this somehow kills cells. "Since Rhes is highly found in the corpus striatum, clumping somehow protects cells in other tissues of the body from dying," says Subramaniam.

Subramaniam and the rest of Snyder's research team currently are exploring whether removing Rhes from mice with Huntington's disease can slow or stop brain cells from dying.

"Now that we've uncovered the role of Rhes, it's possible that drugs can be designed that specifically target Rhes to treat or even prevent the disease," says Snyder.

Source: Johns Hopkins Medical Institutions