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Study points to drug target for Huntington's disease

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Huntington's disease attacks the part of the brain that controls movement, destroying nerves with a barrage of toxicity, yet leaves other parts relatively unscathed.

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have established conclusively that an activating protein, called "Rhes," plays a pivotal role in focusing the toxicity of Huntington's in the striatum, a smallish section of the forebrain that controls body movement and is potentially involved in other cognitive functions such as working memory.

"Our study definitively confirms the role of Rhes in Huntington's disease," said TSRI Assistant Professor Srinivasa Subramaniam, who led the study. "Our next step should be to develop drugs that inhibit its action."

The study was published recently online ahead of print by the journal *Neurobiology of Disease*.

In an earlier study, Subramaniam and his colleagues showed that Rhes binds to a series of repeats in the huntingtin protein (named for its association with Huntington's disease), increasing the death of neurons. The new study shows deleting Rhes significantly reduces behavioral problems in animal models of the disease.

In addition, the study took the research further and revealed the effects

of adding Rhes to the cerebellum, a brain region normally not affected in Huntington's.

Remarkably, Huntington disease animals injected with Rhes experienced an exacerbation of motor issues, including loss of balance and coordination. Subramaniam and his colleagues also found lesions and damaged neurons in the cerebellum, confirming Rhes is sufficient to promote toxicity and showing that even those regions of the brain normally impervious to damage can become vulnerable if Rhes is overexpressed.

"Perhaps the biggest question to emerge from this study is whether Rhes is a good drug target for Huntington's disease," Subramaniam said. "The short answer is 'yes.' Drugs that disrupt Rhes could alleviate Huntington's pathology and motor symptoms."

"Many Huntington's disease patients experience psychiatric-related problems, such as depression and anxiety," added Supriya Swarnkar, the first author of the study and a member of Subramaniam's lab. "But it's unclear whether they are the cause or consequences of the disease. We think, by targeting Rhes, we might block the initiation of Huntington's, which we predict would afford protection against psychiatric-related problems as well."

More information: Ectopic Expression of the Striatal-enriched GTPase Rhes Elicits Cerebellar Degeneration and an Ataxia Phenotype in Huntington Disease, www.sciencedirect.com/science/ … ii/S0969996115001850

Provided by The Scripps Research Institute