MedicalXpress

Novel method results in promising drugs for Huntington's disease therapeutics

January 26 2011

Huntington's disease (HD) is an incurable progressive neurodegenerative genetic disorder which affects motor coordination and leads to cognitive decline and dementia.

The disease pathology stems from a mutation in the huntingtin (Htt) gene which results in the accumulation of toxic proteins leading to neuronal cell death. Earlier studies have clearly implicated caspases, enzymes that break down cells, as key players in the cascade of events involved in HD neuronal death. Now scientists have identified three small molecules that inhibit the activity of those caspases, suppressing toxicity and rescuing neurons from cell death in cell culture.

The research, which appears in the November 24th edition of Chemistry and Biology, was led by both Buck Institute faculty member Lisa Ellerby, Ph.D. and Yale University faculty member Jonathan Ellman, Ph.D. Dr. Ellerby is doing follow up studies in a mouse model of the disease.

Dr. Ellerby said a substrate based screening method was used to identify compounds that reacted with caspases. Based on those reactions, Jonathan Ellman, Ph.D., from the Yale University Department of Chemistry, converted the compounds to caspase inhibitors.

Dr. Ellerby said that the inhibitors are based on properties of a drug which had entered Phase I clinical trials for the treatment of human liver preservation injury. "These molecules shows particular promise," said

Ellerby. "They cross the blood-brain barrier and acts selectively to block the processes involved in HD." Dr. Ellerby said the caspase inhibitors both suppressed the proteolysis of Htt and rescued HD neurons that have begun to undergo cell death.

"We believe this is going to help us move the field forward because now we can test these compounds in live animals," said Dr. Ellerby. "Up until this point we have not identified a caspase inhibitor that has acted selectively against the toxic effects of the Htt mutation."

There is a desperate need for a treatment for HD. Symptoms of the disease usually begin to occur in middle age; patients are often totally incapacitated prior to death. The worldwide prevalence of HD is 5-10 cases per 100,000 people; the rate of occurrence is highest in peoples of Western European descent.

Provided by Buck Institute