New drugs target delay of Huntington's symptoms

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(Medical Xpress) -- McMaster researchers have discovered a new drug target that may be effective at preventing the onset of Huntington's disease, working much the same way heart medications slow the progression of heart disease and reduce heart attacks.

Their landmark research discovered a family of kinase inhibitor drugs - that all target one enzyme called IKK beta kinase - as effective for Huntington's.

The drug restores a critical chemical change that should occur in the huntingtin protein, but does not occur in people with Huntington's disease.

The research appears in the May 29 online edition of *Nature Chemical Biology*.

"It is the first time anyone has identified drugs that affect how the huntingtin protein gets modified at one critical site, and through what pathway," said Ray Truant, professor in the Department of Biochemistry and Biomedical Sciences of the Michael G. DeGroote School of Medicine at McMaster.

Huntington's disease, which impacts one in 4,000 Canadians, is an inherited disease that causes certain nerve cells in the brain to waste away. People are born with a defective gene, but symptoms usually don't appear until middle age. Early symptoms include depression and

cognitive changes, with later symptoms including uncontrolled movements, clumsiness and balance problems. At some point patients may have difficulty walking, talking or swallowing. There is no specific treatment for the disease.

Currently kinase inhibitor drugs form a family of successful, new generation drugs that are coming on the market or have been approved for a wide range of diseases including stroke, arthritis and cancer.

The McMaster researchers are currently looking at inhibitors that can cross the blood to brain barrier, before starting preliminary trials. If successful, human clinical trials are five or more years away.

Truant and Randy Singh Atwal, a PhD graduate, discovered the huntintin protein has an essential role in chemical stresses relating to human aging and the protein is not properly modified in response to these stresses during Huntington's Disease.

"This is one explanation as to why it takes until middle age for Huntington's to develop in most patients, because the role of the huntingtin protein is more critical as a person ages," said Truant.

The research is supported by the Canadian Institutes of Health Research, the not-for- profit Cure for Huntington's Disease Initiative Inc., and the Toronto-based Krembil Family Foundation. Truant is chair of the Huntington Society of Canada's scientific advisory board.

"These new results are extremely important because they may help to delay the progression of Huntington's disease," said Dr. Anthony Phillips, scientific director of the Canadian Institutes of Health Research (CIHR) Institute of Neurosciences, Mental Health and Addiction. "CIHR is proud to support researchers who devote their time to look into this genetic brain disorder that has such challenging effects on individuals

and their families in Canada."

More information: Kinase inhibitors modulate huntingtin cell localization and toxicity, *Nature Chemical Biology* (2011) doi:10.1038/nchembio.582

Abstract

Two serine residues within the first 17 amino acid residues of huntingtin (N17) are crucial for modulation of mutant huntingtin toxicity in cell and mouse genetic models of Huntington's disease. Here we show that the stress-dependent phosphorylation of huntingtin at Ser13 and Ser16 affects N17 conformation and targets full-length huntingtin to chromatin-dependent subregions of the nucleus, the mitotic spindle and cleavage furrow during cell division. Polyglutamine-expanded mutant huntingtin is hypophosphorylated in N17 in both homozygous and heterozygous cell contexts. By high-content screening in live cells, we identified kinase inhibitors that modulated N17 phosphorylation and hence huntingtin subcellular localization. N17 phosphorylation was reduced by casein kinase-2 inhibitors. Paradoxically, IKKβ kinase inhibition increased N17 phosphorylation, affecting huntingtin nuclear and subnuclear localization. These data indicate that huntingtin phosphorylation at Ser13 and Ser16 can be modulated by small-molecule drugs, which may have therapeutic potential in Huntington's disease.

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