Small Molecules Mimic BDNF

The gene for brain derived neurotrophic factor (BDNF) is down regulated in Huntington's Disease. BDNF protects neurons and facilitates the growth of new ones and its lowered level in the brains of HD patients is thought to be a major pathology of the disease.

BDNF is a protein which means that it cannot cross the blood brain barrier and if taken orally would simply be digested. There are a number of potential treatments in the pipeline which are designed to get the brain to boost its levels of BDNF.

Dr. Frank Longo of Stanford University and colleagues from the University of California at San Francisco screened over one million compounds and discovered four chemically distinct compounds which mimic BDNF in some important ways. One or more of these compounds may be suitable for further drug development that could eventually result in a treatment for Huntington's Disease.

BDNF activates the tropomyosin-related kinase B (TrkB) and promotes the survival and differentiation of neurons as well as synaptic function. Trks cause phosphate molecules to be added to certain tyrosines in the cell, thereby activating cellular signaling. It also interacts with P75, a receptor for BDNF (and the other neurotrophins). In contrast to the Trks, the functions of P75 are less well understood and there is a concern that activating it might cause problems with pain.

The four compounds activate TrkB, but not the other Trks and not P75 so they are target specific. One of the compounds was selected for further study and it was found that it activated the downstream pathways associated with stress resistance and cell survival. The compound was used to treat various cell models of neurodegenerative disease and brain injury. For Huntington's, the neurotoxic compound quinolinic acid was used because the damage it causes acutely resembles the damage that is caused over time by HD. In all models, the compound increased cell survival.

In addition, the compound was used to treat mice whose brains had been injured. The treated mice did much better on the rotarod, a measure of motor performance, than those who were not treated.

More work with the compounds and drug development need to be done as well as preclinical studies before a clinical trial could result from this discovery. However, there compounds appear to have potential.

"These small molecules could be the basis of drugs that provide entirely new avenues of treatment for a large number of neuropsychiatric disorders such as Alzheimer's, Huntington's and depression," said Frank Longo, MD, PhD, professor and chair of neurology and senior author of the study.

"BDNF is a dominant and critically important molecule in the central nervous system," said neurologist Dale Bredesen, MD, a professor and founding president at the Buck Institute for Aging Research in Novato, Calif., who was not involved in the study but is familiar with the research. "This is an important study. It's a first step in being able to develop molecules for human studies that are going to be valuable for a number of conditions, including neurodegenerative conditions and head trauma."

Reference:

Stephen M. Massa, TaoYang, Youmei Xie, Jian Shi, Mehmet Bilgen, Jeffrey N. Joyce, Dean Nahama, Jayakumar Rajadas, and Frank M. Longo. **Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents.** Journal of Clinical Investigation 2010 Apr 19 [Epub ahead of print]

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