Axonal transport impaired in HD

Researchers at the University of Illinois at Chicago College of Medicine have identified the mechanism by which axonal transport is impaired in neurons in Huntington's disease. Using mouse, squid, and cell models of HD, Dr. Scott Brady and Dr. Gerardo Morfini and colleagues found that the HD protein activates an enzyme called JNK (for cJun N-terminal kinease) which causes the impairment.

Axons are nerve fibers which project from the neuron and carry electric impulses. The longest axons in the human body are those of the sciatic nerve which run from the base of the spine to the big toes of each foot. Axons in the brain are much smaller of course but are still many times longer than the body of the neuron.

Axonal transport is critical for the survival of neurons. Proteins are synthesized in the cell body and then are transported in microtubulins or 'tracks' which run along axons to the synapses, the junctions through which neurons signal to each other. Vesicles containing neurotransmitters are also carried to the synapses for release. When the transport system becomes impaired, synapases and axons become dysfunctional, signaling is reduced, and the cell begins to die.

The specific form of JNK which does the damage is JNK3 which is found in the brain and testes. JNK3 phosphorylates kinesin-1, the motor protein of the axonal transport system which moves the cargo toward the ends of the axons. Phosphorylation reduces the ability of kinesin-1 to bind to the microtubules, thus impairing transport.

If the mutant protein impairs such a critical function as axonal transport, then why do neurons remain healthy for years? As we age, this function becomes less efficient. "If you take a hit when you're very young, you still are making more and transporting more proteins in each neuron than you need," Dr. Brady said. "But as you get older and older, the neuron produces and transports less. Each hit diminishes the system further. Eventually, the neuron falls below the threshold needed to maintain cell health."

Dr, Brady

Presymptomatic HD mice were found to have impairment of axonal transport, suggesting that this is an early pathology in the disease. The researchers have concluded that inhibiting JNK activation is a promising therapeutic target.

Dr. Brady and his colleagues have also found impairment of axonal transport in Alzheimers and other neurodegenerative diseases. "There is a common theme and a common Achilles heel of the neuron that underlies all these diseases," Dr. Brady said. "We've invented a word, dysferopathy, (from the Greek 'fero', to carry or transport) for these adult-onset neurodegenerative diseases. All have disruption of the axonal transport system in common."

Reference:

Gerardo A. Morfini, Yi-Mei You, Sarah L. Pollema, Agnieszka Kaminska, Katherine Liu, Katsuji Yoshioka, Benny Bjorkblom, Elearnor T Coffey, Carolia Bagnata, David Han, Chun-Fang Huang, Gary Banker, Custavo Pigino, and Scott T. Brady. **"Pathogenic huntingtin inhibits fast axonal transport by activating JNK3 and phosphorylating kinesin."** Nature Neuroscience 2009 Jun 14. [Epub ahead of print]

University of Illinois at Chicago Medical College press release.

- *Marsha L. Miller, Ph.D., June 19, 2009*