Caspase Inhibitors with Therapeutic Potential Identified and Optimized

Dr. Jonathan Ellman

The HD community has been hoping to hear news of a safe and effective caspase six inhibitor ever since Dr. Michael Hayden reported that caspase six resistant mice with the HD gene do not develop Huntington's Disease. A research team led by Buck Institute faculty member Lisa Ellerby, Ph.D. and Yale University faculty member Jonathan Ellman, Ph.D. has developed three novel pan-caspase inhibitors that block proteolysis (fragmentation) of the HD protein at caspase 3 and caspase 6 sites.

The word caspase comes from cysteine-aspartic-acid-proteases. Caspases are enzymes which are used in apoptosis, programmed cell death. There are various caspases that initiate the process, that cleave proteins and that actually 'execute' the cell. Apoptosis is a necessary process in development and also in destroying tumors. Unfortunately, apoptosis is also implicated in neurodegenerative disorders. Apoptosis is triggered by cellular stress, especially mitochondrial stress, and this is known to occur with Huntington's and the various other neurodegenerative disorders. Caspase six cleaves the HD protein into toxic fragments which enter the nucleus of neurons and interfere with gene transcription.

In the Hayden study, HD mice were also engineered to be resistant to caspase six cleavage and they did not experience neurodegeneration. This indirect strategy was used rather than testing them with a caspase six inhibitor since the existing ones were based on peptides and did not cross the blood brain barrier. The Ellerman-Ellerby research team used a substrate based fragment approach called substrate activity screening (SAS) to identify weak-binding nonpeptide fragments that they then optimized to increase potency.

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 show particular promise. They cross the blood-brain barrier and act 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.

The study looked at striatal and cortical neurons from an HD rat model. Dr. Ellerby is already testing these compounds in animal models of Huntington's Disease. "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."

If Dr. Ellerby finds one of the inhibitors to be safe and effective in an HD mouse model, this would be proof of principle that the therapeutic strategy is worth pursuing for people with the HD gene.

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- *Marsha L. Miller, Ph.D., January 21, 2011*