

Synaptic Activity, Extrasynaptic Activity, and Memantine

Coalition researcher Dr. Michael R. Hayden teamed up with Dr. Stuart Lipton, developer of the glutamate stabilizer memantine, to test its effects in cell and mouse models of Huntington's Disease. Memantine is used to treat Alzheimer's Disease. Working with a cell model of the disease, the researchers and their colleagues examined electrical activity associated with N-methyl-D-aspartate (NMDA) receptors. They found that normal synaptic activity (where neurons communicate with each other through electrical impulses) protects the brain from the misfolded HD protein but excessive extrasynaptic activity enhances the HD protein's toxic effect. This is the first time researchers have linked the electric activity of the synapses to protein folding.



Dr. Hayden

They then tested a low dose and a high dose of memantine in the HD mouse. Low doses reduced the extrasynaptic activity but not the normal synaptic activity and treated the disease. High doses actually increased pathology because they blocked the protective, normal synaptic activity as well as the extrasynaptic activity.

Where does this extrasynaptic activity come from, both in the cell culture used in the study and in the brain? There is a pool of glutamate within the cell which is used in metabolism. They speculate that neurons infected with the HD protein may be leaking the glutamate. Further, glutamate released from astrocytes is known to cause extrasynaptic activity in HD.

These findings may explain why past clinical trials with glutamate blockers failed. While blocking extrasynaptic activity is neuroprotective, blocking normal synaptic activity is toxic so no net benefit was obtained.

The mechanisms that were found to cause the neuroprotective effect and the toxic effect link the new research to previous studies. The cumulative research answers some key questions about how the HD protein does its damage.

They found that normal synaptic activity induces aggregation through a T complex-1 (TCP-1) ring complex (TRiC)-dependent mechanism. The soluble HD protein is more toxic than the aggregates.

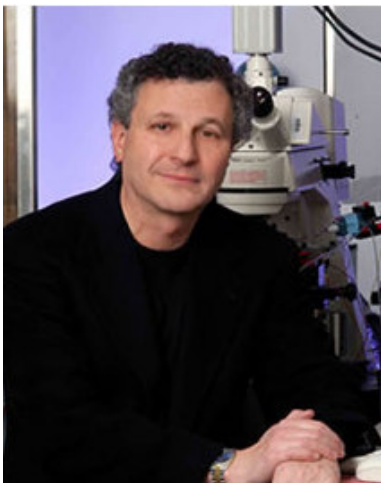
The extrasynaptic activity impairs the normally protective CREB-PGC1-alpha cascade. The Cyclic AMP response element-binding protein (CREB), along with the CREB-binding protein (CBP) which binds with phosphorylated CREB, triggers the upregulation of the neuroprotective PGC1-alpha pathway. They also found that RNAi knockdown of TCP will cause the same result. Low doses of memantine restored PGC1-alpha.

In 2000, Dr. Leslie Thompson and colleagues showed that the HD protein interacts with CBP and represses gene transcription. In 2001, Dr. Christopher Ross and colleagues

found the CBP was dislocated from its normal nuclear location and that overexpression rescued cells from neurotoxicity. In 2006, he found that it was the depletion of CBP rather than its inclusion in aggregates that directly caused neurotoxicity.

In 2006, research by Dr. Weydt, Dr. Albert LaSpada, and other colleagues showed that the PGC-1 alpha gene is downregulated in the brains of Huntington's patients. They were led to look at the gene after discovering that the R6/2 HD mice have a below normal body temperature which continues to drop as the disease progresses. Working independently, another team of researchers from Massachusetts General and New York University Medical School lead by Dr. Dimitri Krainc found that transcription of PGC-1 is repressed by the HD protein which leads to mitochondrial dysfunction. Delivery of PGC-1 to transgenic HD mice is neuroprotective while crossing the HD mice with PGC-1 null mice results in more severe symptoms of Huntington's.

Drs Hayden and Lipton also found a connection with another known HD pathology. They showed that extrasynaptic activity increases the amount of rhes, a protein found mainly in the striatum, while low doses of memantine decrease it. This is important because a recent study conducted by Dr. Solomon Snyder and colleagues at Johns Hopkins found that rhes binds to the HD protein and causes toxicity. The mechanism by which this occurs is sumoylation. SUMO is a Small Ubiquitin-like Modifying protein. The SUMO protein is attached or detached to another protein as part of a post-translational process which modifies the protein's function. Sumoylation is known to contribute to HD pathology. In 2004, Dr. Joan Steffan and colleagues found that sumoylation decreases aggregation of the HD protein (the soluble HD protein is more toxic than the aggregates), masks a signal for the HD protein to stay in the cytoplasm, and promotes the dysregulation of gene transcription in the nucleus of the cell.



"Chronic neurodegenerative diseases like Huntington's, Alzheimer's and Parkinson's are all related to protein misfolding," said Dr. Lipton. "We show here, for the first time, that electrical activity controls protein folding, and if you have a drug that can adjust the electrical activity to the correct levels, you can protect against misfolding. Also, this verifies that appropriate electrical activity is protective, supporting the 'use it or lose it theory' of brain activity at the molecular level. For example, this finding may explain why epidemiologists have found that 'using' your brain by performing crossword puzzles and other games can stave off cognitive decline in diseases like Alzheimer's."

Dr. Lipton

"For a long time it's been known that excitotoxicity is an early marker of Huntington's disease," said Dr. Hayden. "However, now we have dissected the mechanism by which this happens, particularly focusing on NMDA receptors outside the synapse. This creates

novel therapeutic opportunities to modulate these receptors with potential protective effects on nerve cells."

Research like this is very important because it links various pathological mechanisms which have been known to occur in Huntington's Disease and because it identifies a major therapeutic target for which there is already an FDA approved treatment. International clinical trials of memantine are now being planned.

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- Marsha L. Miller, Ph.D., December 8, 2009