

More on Extrasynaptic Activity and Memantine in the HD Mice

Dr. Michael Hayden and his colleagues have reported additional findings from their study of extrasynaptic activity and its role in HD pathology.

We previously reported on an earlier study that found that normal synaptic activity involving the NMDA (N-methyl-D-aspartate) receptors is neuroprotective while extrasynaptic activity enhances the toxic effect of the HD protein. (see <http://www.hdsa.org/images/content/1/2/12614.pdf>). The new study presents evidence that there are more extrasynaptic NMDA receptors in the striatum of the YAC128 HD mice.



"Previous work in cell cultures showed that NMDA receptors located within the synapse can have beneficial effects on brain cells, whereas NMDA receptors outside the synapse, called 'extra-synaptic NMDA receptors,' have a detrimental effect," says Dr. Lynn Raymond, a professor in the UBC Department of Psychiatry, a member of the Brain Research Centre at UBC Hospital, and co-director of the Huntington's Disease Medical Clinic.

"Our study shows an increase in the number of extrasynaptic NMDA receptors, shifting the balance between these opposing cellular mechanisms in animal models of early stages of Huntington's disease," Raymond says.

The earlier study found that memantine, an Alzheimer's drug, which preferentially blocks helped later stage HD YAC128 mice. The HD mice were given low doses of memantine from the age of two months with the result that motor performance and striatal volume were also improved at twelve months.

This study found that earlier defects were remedied as well. At four months, the YAC128 mice exhibit decreased CREB activity in the striatum and an impaired ability to learn motor skills. The memantine prevented these deficits.

"Memantine in low dose works by preferentially blocking the activity of NMDA receptors outside the synapse," says Dr. Michael Hayden, director of the Centre for Molecular Medicine and Therapeutics, professor in the UBC Department of Medical Genetics, and co-author on the study.

"It was previously shown to reverse deficits and damage in late stages of animal models of Huntington's disease, but we found it could improve learning and cell survival signaling even at early stages of the disease," says Hayden. "A small human clinical trial of memantine for Huntington's disease has also recently shown positive effects. Larger, international clinical trials are now being planned."

"Memantine's beneficial effects appear to be dose-specific," Raymond adds. "Before it can be prescribed to treat Huntington's disease, we need to know how to determine appropriate dosing and whether it interferes with other essential cellular and brain functions."

In the first study, the results tied the extrasynaptic pathology to other known pathologies of the disease, including the impairment of the normally protective CREB-PGC1- α cascade resulting in the dysregulation of gene transcription and in the increase in rhés, a protein that binds to the HD protein and causes toxicity.

The new study also reports a connection to caspase 6. In 2006, Dr. Hayden and colleagues reported that caspase six resistant mice with the HD gene do not develop Huntington's Disease. In this study, they did an electrophysiological study of the caspase 6 resistant mice to see if they had increased extrasynaptic activity. They did not and since they are identical to the YAC128 HD mice with the exception of a point mutation that makes them resistant to caspase six, this suggests that caspase six mediated cleavage of the HD protein is necessary for the increase in extrasynaptic activity to occur.

This is landmark work, linking neurotransmission between cells to multiple pathologies within the cell. It also clarifies the excitotoxicity theory of Huntington's disease, a theory which had much data to support it but which has not resulted in a treatment.

The excitotoxicity theory is that excessive stimulation of the NMDA receptors with the neurotransmitter glutamate results in a calcium overload which damages the cell and eventually causes cell death and that this is a major pathological process in Huntington's Disease. Various glutamate blockers were put into clinical trials but none were found to be effective. Glutamate is an important neurotransmitter and is needed for synaptic plasticity (the foundation of learning and memory), gene transcription, and cell survival so ordinary activity must be maintained.

The study clarifies that it is the activity outside of the receptors at the synapses where cells normally communicate with each other that is the problem. The extrasynaptic activity is a good target for treatment and memantine appears to be a good candidate drug based on preclinical work and early clinical trials in Huntington's patients.

Dr. Hayden received support from the HDSA through the Coalition for the Cure Program. Team member Dr. Austen Milnerwood received a joint HDSA/HSC fellowship for this project.

References:

Rona K. Graham, Yu Deng, Elizabeth J. Slow, Brendan Haigh, Nagat Bissada, Ge Lu, Jacqueline Pearson, Jacqueline Shehadeh, Lisa Bertram, Zoe Murphy, Simon C. Warby, Crystal N. Doty, Sophie Roy, Cheryl L. Wellington, Blair R. Leavitt, Lynn A. Raymond, Donald W. Nicholson, and Michael R. Hayden. **"Cleavage at the Caspase-6**

Site Is Required for Neuronal Dysfunction and Degeneration Due to Mutant Huntingtin.” Cell, Vol 125, 1179-1191, 15 June 2006.

Austen J. Milnerwood, Clare M. Gladding, Mahmoud A. Pouladi, Alexandra M. Kaufman, Rochelle M. Hines, Jamie D. Boyd, Rebecca W.Y. Ko, Oana C. Vasuta, Rona K. Graham, Michael R. Hayden, Timothy H. Murphy, and Lynn A. Raymond “**Early Increase in Extrasynaptic NMDA Receptor Signaling and Expression Contributes to Phenotype Onset in Huntington’s Disease Mice.**” Neuron 65, 178–190, January 28, 2010.

Shu-ichi Okamoto, Mahmoud A.Pouladi, Maria Talantova, Dongdong Yao, Peng Xia, Dagmar E. Ehrnhoefer, Rameez Zaidi, Arjay Clemente, Marcus Kaul, Rona K. Graham, Zhang, H-S Vincent Chen, Tong, Hayden, and Stuart A. Lipton. "**Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin.**" Nature Medicine 2009 Nov 15. [Epub ahead of print].

- *Marsha L. Miller, Ph.D., January 31, 2010*