

## **An ampakine upregulates BDNF and improves memory in the HD knock-in mice**

Dr. Gary Lynch and colleagues have been researching memory deficits in the HD knock-in mouse and investigating whether a class of drugs called ampakines could ameliorate them. In their latest study, an ampakine upregulated BDNF and improved memory deficits in the HD knock-in mouse model.

Brain derived neurotrophic factor (BDNF) is downregulated in the brains of HD patients and in mouse models of the disease. BDNF protects neurons and facilitates the growth of new ones. It also plays an important role in long term memory. BDNF signaling is part of a system of synaptic changes that encode long term memories. It promotes theta burst stimulation which in turn induces actin polymerization which stabilizes long term potentiation. Long term potentiation involves a change in the electrical properties of neurons and is a necessary component of memory.

Dr Lynch and colleagues have found that actin polymerization and long term potentiation are both impaired in the HD knock-in mice. It seems likely then that the decrease in BDNF in Huntington's Disease could be responsible for the memory problems that HD patients experience. BDNF does not cross the blood barrier so a therapeutic strategy to address the problem would involve discovering or developing a drug that increases it.



SSRI (serotonin reuptake inhibitor) antidepressants are known to increase BDNF and one of them, citalopram (Celexa), is currently in clinical trials to see if it improves cognition. Another possible drug is an ampakine. Ampakines are a class of drugs which bind to AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) type glutamate receptors which mediate synaptic transmission in the central nervous system.

The researchers used an ampakine that has a short half life (the time it takes for a drug to lose half of its pharmacological activity). A short half life can mean fewer side effects but lesser effectiveness. In this case, the ampakine stimulated BDNF which has a much longer half life. They found that twice daily injections of the ampakine upregulated BDNF, normalized actin polymerization, and stabilized long term potentiation in the knock in mice. Memory deficits were rescued in while motor behavior remained unchanged.

“Brain-derived neurotrophic factor (BDNF), is reduced in Huntington's disease. We know that BDNF plays an essential role in maintaining the health of the brain,” commented Dr. Lynch. “And our studies now demonstrate that we can restore levels of BDNF by treating mice with an AMPAKINE, which reverses the memory impairments.”

In this study, the focus was on memory and other symptoms in the mice. Further studies are needed to determine if ampakines have a neuroprotective effect and actually treat the disease itself. This is a possibility, but even if they do not, a treatment to improve

cognition in HD patients is not currently available and would be a welcome addition to symptomatic treatments.

The ampakine used in the study is owned by Cortex Pharmaceuticals which was co-founded by Dr. Lynch. Cortex has a different ampakine currently in a Phase IIb clinical trial for Alzheimer's and a portfolio of a variety of structurally different ampakines. Some of their other ampakines are in clinical trials for depression, ADHD, and respiratory distress. If ampakines continue to look promising for HD, the information gained from trials with other diseases can speed the time necessary to move through the drug pipeline for Huntington's.

Mark A. Varney, President and CEO stated that, "Professor Lynch's studies in mice support the rationale for Cortex to develop AMPAKINE molecules to address the memory deficits in patients suffering from Huntington's disease. Also, the link to BDNF may play an important role in other neurodegenerative diseases such, as Alzheimer's Disease."

## **Reference**

Danielle A. Simmons, Christopher S. Rex, Vijay Pandeyarajan, Vidm Fedulov, Christine M. Gall, and Gary Lynch . "**Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice.**" Proceedings of the National Academy of Sciences of the United States of America 2009 Mar 24;106(12):4906-11.

- *Marsha L. Miller, Ph.D., April 7, 2009*