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Promising approach to slow brain degeneration in a model of Huntington's disease

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Research presented by Dr. Lynn Raymond, from the University of British Columbia, shows that blocking a specific class of glutamate receptors, called extrasynaptic NMDA receptors, can improve motor learning and coordination, and prevent cell death in animal models of Huntington disease.

As Huntington disease is an inherited condition that can be detected decades before any clinical symptoms are seen in humans, a better understanding of the earliest changes in brain cell (neuronal) function, and the molecular pathways underlying those changes, could lead to preventive treatments that delay the onset of symptoms and neurodegeneration.

"After more than a decade of research on the pre-symptomatic phase of Huntington disease, markers are being developed to facilitate assessment of interventional therapy in individuals carrying the genetic mutation for Huntington disease, before they become ill. This will make it possible to delay onset of disease," says Dr. Raymond.

These results were presented at the 2014 Canadian Neuroscience Meeting, the 8th annual meeting of the Canadian Association for Neuroscience - Association Canadienne des Neurosciences (CAN-ACN), held in Montreal, May 25-28.

The neurotransmitter glutamate has long been known to promote cell death, and its toxic effects occur through the action of a family of receptors known as the NMDARs (N-methyl-D-Aspartate ionotropic glutamate receptors). Unfortunately, treating disorders of the nervous system by blocking NMDARs has not been successful because such treatments have numerous side effects. A recent hypothesis based on work from many scientists suggests that NMDARs located in different regions at the surface of neurons may have opposite effects, which would explain why blocking all NMDARs is not a good treatment option.

A synapse is a structure that allows one neuron to connect to another neuron and pass an electrical or chemical signal between them. Many receptors for neurotransmitters are located in synapses, as these are the main area where these chemical signals are transmitted. However, receptors can also be found outside the synapse, and in this case are called extra-synaptic receptors. Many recent studies have revealed that NMDARs located at synapses act to increase survival signaling and promote learning and memory, whereas extra-synaptic NMDARs shut off survival signaling, interfere with learning mechanisms, and increase cell death pathways.

Dr. Raymond and her team were able, by using a drug that selectively blocks extra-synaptic NMDARs early, before the appearance of any symptoms, to delay the onset of Huntington-like symptoms in a mouse model of the disease. These promising results could lead to new treatment avenues for Huntington patients, and delay the appearance of symptoms. "The drug we used, memantine, is currently being used to treat moderate-stage Alzheimer disease patients. Our results suggest that clinical studies of memantine and similarly-acting drugs in Huntington disease, particularly in the pre-symptomatic stage, are warranted,"says Dr. Raymond.

Extra-synaptic NMDARs have also been shown to be involved in other neurodegenerative diseases, such as Alzheimer disease, and in damage caused by traumatic brain injury and some forms of stroke. These results therefore suggest novel treatment avenues for many conditions in which neurons degenerate and die, a new way to protect neurons before the appearance of symptoms of neurodegeneration.

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