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Alteration of brain protein regulates learning

DALLAS – Aug. 17, 2005 – Researchers at UT Southwestern Medical Center have identified a biochemical switch that affects how neurons fire in a part of the brain associated with learning, findings that may aid in understanding schizophrenia and Alzheimer's disease.

The research sheds new light on the action of reelin, a protein known to be important in the nervous system. During development, reelin sends cues to migrating neurons, telling them where they're supposed to go. In adult mice, reelin has recently been implicated in the formation of memories, and reduced production of reelin has been associated with schizophrenia in humans.

In a report published in the Aug.18 issue of the journal *Neuron*, Dr Joachim Herz, professor of molecular genetics and a member of the Center for Basic Neuroscience at UT Southwestern and the paper's senior author, studied an area of the brain called the hippocampus, which is important for learning. He and his colleagues focused on the interaction of reelin and two other molecules, Apoer2 and the NMDA receptor.

In the nervous system the NMDA receptor is embedded in the membrane of synapses – gaps between nerve cells – where it is involved in receiving signals from other nerve cells. Apoer2 is another receptor which is associated with the NMDA receptor. When reelin encounters the cell, it attaches to Apoer2, which then boosts the activity of the NMDA receptor by promoting a chemical modification of the part of the NMDA receptor inside the cell. The result of this modification is that signals being received by the nerve cell are amplified – and better reception means better learning.

This transition in the primary function of Apoer2, from guiding neurons in the embryonic brain to regulating synaptic signaling, occurs around the time of birth. A small string of amino acids, the building blocks of proteins, gets added near one end of Apoer2 and is essential for this new function. Adding the new amino acids is similar to cutting a rope, splicing in a short portion, and lashing the ends in place.

This longer form of Apoer2 is necessary for reelin to act upon the NMDA receptor, Dr. Herz and his colleagues found. When reelin binds to the longer Apoer2, the NMDA receptor alters its

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structure and actions, resulting in the strengthening of the signals the nerve cells receive.

When the researchers created mutant mice in which Apoer2 was missing the spliced portion, they found that the mice had difficulties with learning and memory. They were slow to learn where a hidden platform was in murky water, among other tasks, and when the electrical activity of neurons was measured in the hippocampus of these mice there was no longer any detectable reaction to reelin.

Thus, the extra string of amino acids in Apoer2 seems to work like a switch that patches the reelin signal through to the NMDA receptor and, thereby, plays a central role for learning and memory in the whole animal.

In addition to reelin, Apoer2 binds to a protein called ApoE. One form of this molecule, called ApoE4, has been shown to substantially increase the risk of Alzheimer's disease in older people. Understanding how ApoE4 functions in the brain and interacts with ApoE receptors, such as Apoer2, is critical for gaining further insight into the mysterious mechanisms that cause this debilitating neurodegenerative disease, Dr. Herz said. The loss of synapses that occurs in Alzheimer's disease is the primary cause for the dementia in the afflicted patients.

"Our findings put ApoE receptors at the heart of the matter," said Dr. Herz, who holds the Thomas O. Hicks Family Distinguished Chair in Alzheimer's Disease Research.

Other UT Southwestern researchers involved in the study were Dr. Uwe Beffert, postdoctoral researcher in biophysics and molecular genetics and lead author of the study; Dr. Robert Hammer, professor of biochemistry; Dr. Wei-Ping Li, assistant professor of cell biology; Andre Durudas, student research assistant in internal medicine; and Irene Masiulis, student research assistant in biophysics and molecular genetics. Researchers from Vanderbilt University, Baylor College of Medicine and the Center for Neuroscience in Freiburg, Germany, also participated.

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