SOUTHWESTERN NEWS

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EMBARGOED UNTIL 11 A.M. CDT WEDNESDAY, APRIL 7, 2004

Lack of specific brain protein causes marked deficits in learning, memory

DALLAS – April 7, 2004 – A protein involved in the release of neurotransmitters in the brain is essential to learning and memory in mice, researchers at UT Southwestern Medical Center at Dallas have found.

A study published today in *Neuron* offers the first evidence that lack of this protein – known as *RIM1 alpha* – causes profound deficits in the learning process. The discovery is a major step in understanding the molecular events that underlie learning and memory – complex processes that can be impaired in human neuropsychiatric disorders such as Alzheimer's disease, mental retardation and schizophrenia.

"We found that when you delete this molecule, the mice essentially become incredibly stupid," said Dr. Thomas Südhof, director of both the Center for Basic Neuroscience and the C. Vincent Prothro Center for Research in Basic Neuroscience at UT Southwestern and co-author of the paper.

Researchers hope that further study of the protein's role in learning and memory will lead to potential treatments for some neuropsychiatric disorders.

"This is the first indication that these proteins could be good targets for treatment of specific brain disorders," said Dr. Craig Powell, assistant professor of psychiatry and neurology at UT Southwestern and the study's lead author.

The researchers compared behaviors of normal mice to those of three sets of genetically altered mice – each of which was missing a specific protein involved in releasing neurotransmitters. The mice lacking the *RIM1 alpha* protein, unlike the others, lacked the ability to learn the location of an escape platform in a pool of water despite repeated attempts over several days.

Dr. Eric Nestler, chairman of psychiatry at UT Southwestern and senior author of the study, said another notable finding was that, while the other two sets of genetically altered mice displayed some of the same cellular abnormalities as the *RIM1 alpha* mice, these other mice exhibited no

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behavioral deficits.

"The brain was able to compensate for the loss of these other two proteins, but it was not able to compensate for the lack of *RIM1 alpha*," Dr. Nestler said. "That tells us that *RIM1 alpha* is involved in so many important functions that, when it is missing, gross changes in behavior occur."

Proteins involved in the release of neurotransmitters are known as presynaptic proteins. In the past, postsynaptic proteins, as opposed to presynaptic proteins, were shown to play an active role in learning and memory. Postsynaptic proteins receive the neurotransmitters released by presynaptic proteins.

Dr. Nestler said that some of the abnormalities in learning in the mice lacking *RIM1 alpha* are reminiscent of symptoms commonly seen in people with schizophrenia.

"This could give us new insight into what's going wrong in the brains of people with schizophrenia – a disorder that is still not at all well understood," Dr. Nestler said.

These studies were funded via grants from the National Institute of Mental Health, The National Alliance for Research on Schizophrenia and Depression, and the Howard Hughes Medical Institute.

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