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Specific brain protein required for nerve cell connections to form and function

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Neurons, or nerve cells, communicate with each other through contact points called synapses. When these connections are damaged, communication breaks down, causing the messages that would normally help our feet push our bike pedals or our mind locate our car keys to fall short.

Now scientists at the University of North Carolina at Chapel Hill School of Medicine have shown that a protein called neurexin is required for these nerve cell connections to form and function correctly.

The discovery, made in Drosophila fruit flies may lead to advances in understanding autism spectrum disorders, as recently, human neurexins have been identified as a genetic risk factor for autism.

"This finding now gives us the opportunity to see what job neurexin performs within the cell, so that we can gain a better insight into what can go wrong in the nervous system when neurexin function is lost" said Dr. Manzoor Bhat, associate professor of cell and molecular physiology in the UNC School of Medicine and senior author of the study.

The study, published online September 6, 2007, in the journal *Neuron*, is the first to successfully demonstrate in a Drosophila model the consequences that mutating this important protein may have on synapses.

The research was supported in part by grants from the National Institute of General Medical Sciences, National Institute of Neurological

Disorders and Stroke and the National Institute of Mental Health and funds from the state of North Carolina.

During the last decade, scientists have learned that neurexins are integral to the transmission of chemical signals within the nervous system. Neurexins interact with binding partners called neuroligins to link neighboring nerve cells together so that signals can be sent and received correctly.

Previous attempts to study these proteins in animal models have been challenging. In vertebrates such as mice, three different genes code for the production of certain neurexin proteins. Deleting just one of these genes causes no adverse effects in mouse models, while removing all three is fatal. But fruit flies have only one gene for neurexin, and when Bhat and colleagues deleted the gene, the flies survived — barely.

"Knocking out neurexin basically resulted in a fly with defective nervous system" said Bhat, also a member of the UNC Neuroscience Center and the UNC Neurodevelopmental Disorders Research Center.

First of all, the mutated fruit flies had trouble moving around. When the researchers examined the synapses in these flies, they found that half of them were gone. The synapses that remained were deformed, causing them to send out less chemical signals. The researchers, led by Jingjun Li, a graduate student in neurobiology in the UNC School of Medicine, concluded that neurexin is required for the growth of synapses, for the maintenance of their structure and for their function.

Currently, Bhat and other scientists are working to identify the proteins that neurexin binds to, how they interact, and what sequence of events ultimately results in the organization of synapses within nerve cells. The hope is that such studies in Drosophila will one day clarify the role neurexin plays in learning and memory, ultimately leading to a better

understanding of how defects in this protein can lead to human disorders such as autism, Bhat said.

Source: University of North Carolina at Chapel Hill