MedicalXpress

Scientists identify fundamental brain defect, probable drug target in fragile X syndrome

September 17 2007

Scientists have discovered how the gene mutation responsible for fragile X syndrome--the most common inherited form of mental retardation--alters the way brain cells communicate. In neurons cultured from laboratory rats, the scientists also were able to reverse the effects of the mutation using a drug targeted to the specific site in an upstream pathway of the defect. The finding could lead to the development of human therapies for this previously untreatable condition.

The research was led by Stephen T. Warren, PhD, Timmie professor and chair of human genetics in Emory University School of Medicine, and Gary J. Bassell, PhD, Emory professor of cell biology. It will be reported in the *Proceedings of the National Academy of Sciences* the week of Sept. 17. Lead author is Emory genetics postdoctoral fellow Mika Nakamoto.

"We have now explained the fundamental defect in the brain in fragile X syndrome and, most importantly, found that we can correct this problem in the laboratory," says Dr. Warren. "This is quite exciting, progressing from the identification of the gene in 1991 to now believing we will be able to treat a previously untreatable condition. Our next steps will be to continue screening and identifying the best drugs to try and correct the deficiencies that result from fragile X syndrome."

Fragile X syndrome is caused by a mutation in the FMR1 gene on the X chromosome. A region of the mutated FMR1 gene repeats a trinucleotide sequence of DNA bases--CGG--between 200 and 1,000 times, rather than the normal 6 to 55 repeats in normal individuals. The

abnormal trinucleotide repeats cause the absence of the FMR protein normally produced by the gene.

Dr. Warren and his colleagues led an international team that discovered the FMR1 gene in 1991. They later characterized the FMR protein (FMRP) and developed diagnostic tests for fragile X syndrome. Ever since, their research has focused on identifying the specific consequences of FMRP deficiency in the brain and finding targets for drug therapy.

Previously, Dr. Warren, working with scientists at Brown University, discovered that the absence of FMRP in the mouse model of fragile X syndrome leads to an abnormality in synaptic strength, or the degree by which neurons communicate, that suggested an abnormality of AMPAR receptors on the surface of neurons. These receptors are necessary for neurons to connect with each other at synapses, allowing the communication that leads to learning and memory. Drs. Warren and Bassell discovered that in fragile X syndrome, AMPAR receptors move in and out of the surface neuronal cells more frequently and destabilize the synaptic connections. The Emory scientists and others believe this is the ultimate defect in fragile X syndrome.

Using cultured neurons in the laboratory, manipulated to model fragile X syndrome, the Emory scientists were able to target the mGluR5 receptor with an mGluR5 antagonist--MPEP. Since the mGluR5 receptor is upstream of FMRP and has an opposing influence over the neuron, tempering mGluR5 stimulation should normalize the consequence of the loss of FMRP. Indeed, the Emory scientists found the targeted MPEP therapy rescued the abnormal AMPAR receptor movement on the surface of the FMRP-deficient neurons.

"By adding a drug that antagonizes the mGluR5 receptor and signal, we were able to normalize the AMPAR receptor trafficking, and

presumably allow the neurons to make appropriate synaptic connections," Dr. Warren says. "This gives us great hope that we will be able to develop treatments for patients with fragile X syndrome."

Source: Emory University