

Scientific Articles

MIT Corrects Inherited Retardation, Autism in Mice Research points to potential drug treatment

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Researchers at MIT's Picower Institute for Learning and Memory have corrected key symptoms of mental retardation and autism in mice. The work, which will be reported in the Dec. 20 issue of *Neuron*, also indicates that a certain class of drugs could have the same effect. These drugs are not yet approved by the FDA, but will soon be entering into human clinical trials.

Fragile X syndrome (FXS), affecting 100,000 Americans, is the most common inherited cause of mental retardation and autism. The MIT researchers corrected FXS in mice modeling the disease. "These findings have major therapeutic implications for fragile X syndrome and autism," said study lead author Mark F. Bear, director of the Picower Institute and Picower Professor of Neuroscience at MIT.

The findings support the theory that many of FXS's psychiatric and neurological symptoms—learning disabilities, autistic behavior, childhood epilepsy stem from too much activation of one of the brain's chief network managers—the metabotropic glutamate receptor mGluR5.

"Fragile X is a disorder of excess-excess synaptic connectivity, protein synthesis, memory extinction, body growth, excitability—and remarkably, all these excesses can be reduced by reducing mGluR5," said Bear, a Howard Hughes Medical Institute investigator.

Individuals with FXS have mutations in the X chromosome's FMR1 gene, which encodes the fragile X mental retardation protein, FMRP. The MIT study found that FMRP and mGluR5 are at opposite ends of a kind of molecular seesaw. They keep each other in check, and without FMRP, mGluR5 signals run rampant.

Bear and colleagues study how genes and environment interact to refine connections in the brain. Synapses are the brain's connectors and their modifications are the basis for all learning and memory. There's a growing consensus among researchers that developmental brain disorders such as FXS, autism and schizophrenia should be considered "synapsopathies"—diseases of synaptic development and plasticity (the ability to change in response to experience).

Dendritic spines—little nubs on neurons' branchlike projections—receive many of the synaptic inputs from other neurons. Abnormal spines have long been associated with various forms of human mental retardation. In FXS, spines are more numerous, longer and more spindly than they should be. Thin spines tend to form weak connections.

The research team found that a 50 percent reduction in mGluR5 fixed multiple defects in the fragile X mice. In addition to correcting dendritic spines, reduced mGluR5 improved altered brain development and memory, restored normal body growth, and reduced seizures—many of the symptoms experienced by humans with FXS.

The researchers used genetic engineering to reduce mGluR5, but the same thing could be accomplished by a drug. Although not yet approved by the FDA, mGluR5 blockers are entering into human clinical trials. "Insights gained by this study suggest novel therapeutic approaches, not only for fragile X but also for autism and mental retardation of unknown origin," Bear said.

Earlier this year, MIT Picower Institute researcher Susumu Tonegawa and colleagues reported positive results using a different approach to reversing FXS symptoms. Tonegawa and colleagues identified a key enzyme called p21-activated kinase, or PAK, that affects the number, size and shape of connections between neurons.

Thimerosal (Mercury) Exposure during Pregnancy Linked to Autistic Disorders

WASHINGTON, DC – In the May 2007 issue of the *Journal of Maternal-Fetal and Neonatal Medicine* (<http://tinyurl.com/3533kg>), the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania and Perinatal Societies, and the International Society of Perinatal Obstetricians, a new study, "A Prospective Study of Thimerosal-Containing Rho(D)-Immune Globulin Administration as a Risk Factor for Autistic Disorders," was published by Dr. Mark R. Geier (President, the Genetic Centers of America) and David A. Geier (Vice-President, the Institute of Chronic Illnesses). This new study shows that administration of Thimerosal-preserved Rho(D)-immune globulin preparations during pregnancy significantly increases the risk for offspring developing autistic disorders. This finding is consistent with previously published research by Dr. Amy Holmes, Mark Blaxill, and Dr. Boyd Haley in the *International Journal of Toxicology* (2003), and refutes the recent study funded by Johnson & Johnson (a maker of Rho(D)-immune globulins) that failed to find an association between Thimerosal-preserved Rho(D)-immune globulins and autistic disorders.

Since the late 1980s, Rho(D)-immune globulin preparations have been routinely administered to Rh-negative women in the US during pregnancy at 28 weeks gestation, a prenatal period corresponding to damage occurring in the fetal brain, that has been associated with autistic disorders. Unfortunately, until 2001, some formulations of Rho(D)-immune globulins manufactured for the US market contained Thimerosal, a mercury-containing compound (49.6% mercury by weight). As a result, administration of Thimerosal-preserved Rho(D)-immune globulins exposed Rh-negative pregnant women to bolus doses of mercury ranging from 10.5 to greater than 30 micrograms mercury per administration at critical prenatal developmental periods. In some cases, Rh-negative women received several Rho(D)-immune globulins during their pregnancy. In addition, if the fetus was Rh-positive, the mother was administered another Rho(D)-immune globulin after birth. When that infant was breastfed, then, that infant would receive another significant mercury exposure.

In this new study, the researchers examined a total of 53 non-Jewish Caucasian patients with a diagnosis of an autistic spectrum disorder (ASD), born from 1987 through 2001, who prospectively presented to the Genetic Centers of America for outpatient genetic/developmental evaluations from June 1, 2005 through March 31, 2006. Imaging and laboratory testing were conducted to rule-out other causal factors for their ASDs. As race-matched controls, the frequency of Rh-negativity was determined from 926 non-Jewish Caucasian pregnant women who presented for outpatient prenatal genetics care to the Genetic Centers of America between 1980 and 1989. Children with a diagnosis of an ASD were more than twice as likely to have an Rh-negative mother than the controls. Each ASD patient with an Rh-negative mother was administered a Thimerosal-preserved Rho(D)-immune globulin during her pregnancy. These researchers concluded that their results provide insights into the causal role prenatal mercury exposure may play in some children diagnosed with autistic disorders.

Note: For those who wishing to confirm, whether or not, their child is mercury poisoned, they may want to have a urine porphyrin profile analysis (UPAA) test done. For more information, visit the Coalition for Mercury-free Drugs (CoMeD)'s web site: <http://www.Mercury-freeDrugs.org>

DISCLAIMER - *Beyond the Limits, An Autism Resource Connection provides general information regarding medical research, treatment options, therapies, and nutrition to the autism community. The information comes from a variety of sources (leaders in the field of autism research and physicians with extensive clinical practices) and Beyond the Limits does not independently verify any of it. Nothing written here should be construed as medical advice. Always consult your child's doctor regarding his or her individual needs.*