## Treatment for Fragile X?

Evidence that may point the way to an effective treatment for Fragile X syndrome, the leading inherited cause of mental retardation and a disorder that frequently causes autistic-like symptoms, was recently reported by two research teams.

Sean M.J. McBride and colleagues, noting that studies of mice lacking the gene that is mutated in Fragile X gene showed increased activity of the metabotropic glutamate receptor (mGluR) on the surfaces of neurons, hypothesized that that mGluR overactivity could cause many of the symptoms associated with Fragile X syndrome. To test their theory, the researchers administered MPEP, a drug that block this receptor's activity, to fruit flies lacking the Fragile X gene. They also tested lithium, which affects glutamate receptors.

They report that while fruit flies lacking the Fragile X gene were unable to exhibit normal "conditioned" courtship behavior which is dependent on learning and memory, the flies given MPEP or lithium developed this ability. Further analysis confirmed that this change was due to a reduction in mGluR activity.

The researchers say their findings suggest that "similar modulation of mGluR activity in Fragile X patients should be explored as an approach to ameliorate their cognitive defects and behavioral symptoms."

In more recent research, Q. J. Yan and colleagues examined the effects of MPEP on the seizure susceptibility and "open field activity" of mice bred to serve as models of human Fragile X syndrome. The researchers report that MPEP can reverse susceptibility to audiogenic (sound-induced) seizures, and alters open field activity to the degree that the Fragile X mice are "indistinguishable" from normal wild mice. They conclude, "Modulation of mGluR5 [a specific type of mGluR receptor] signaling may allow amelioration of symptoms of Fragile X syndrome."

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"Pharmacological rescue of synaptic plasticity, courtship behavior, and mushroom body defects in a Drosophila model of fragile X syndrome," Sean M.J. McBride, Catherine H. Choi, Yan Wang, David Liebelt, Evan Braunstein, David Ferreiro, Amita Sehgal, Kathleen K. Siwicki, Thomas C. Dockendorff, Hanh T. Nguyen, Thomas V. McDonald, and Thomas A. Jongens, *Neuron*, Vol. 45, No. 5, March 3, 2005, 753-64. Address: Sean M. J. McBride, Section of Molecular Cardiology, Department of Medicine, Medical Scientist Training Program, Albert Einstein College of Medicine, Bronx, NY 10461, smcbride@aecom.yu.edu.

—and—

"Fruit fly study points to treatment for fragile X syndrome," news release, March 2, 2005.

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"Suppression of two major fragile X syndrome mouse model pheontypes by the mGluR5 antagonist MPEP," Q. J. Yan, M. Rammal, M. Tranfaglia, and R. P. Bauchwitz, *Neuropharmacology*, July 26, 2005 (epub ahead of print). Address: Q. J. Yan, Department of Neurology, St. Luke's-Roosevelt Institute for Health Sciences, Columbia University, New York, NY 10019.

## Study implicates thimerosal in glutamate dysfunction

New research links the mercury-laden vaccine preservative thimerosal to dysregulation of the glutamate system. Glutamate, an excitatory neurotransmitter, is crucial to learning and memory, but when present in excess it can cause widespread neuron damage or death. Glutamate abnormalities are increasingly being implicated as a factor in autism, Fragile X syndrome, and other neurodevelopmental disorders.

> Mutkus and colleagues conclude, "Overall, the study provides direct evidence for the potential of thimerosal to alter glutamate homeostasis in the central nervous system."

Lysette Mutkus and colleagues studied the effects of thimerosal on the expression, function, and transport activity of two types of cellular transporters, GLAST and GLT-1, that remove glutamate from synapses (the spaces between neurons) after its release from neuronal receptors. These transporters must function correctly in "cleaning up" glutamate, in order to keep the glutamate system in proper balance.

The researchers report, "[Our] results indicate that thimerosal is a potent inhibitor of transport activity as measured by D-aspartate uptake." The effect was more pronounced for GLT-1, they say, "and it occurs in the presence of selective changes in mRNA and protein expression of GLAST and GLT-1." They conclude that the ethylmercury in thimerosal directly inhibits transporter activity, and say, "Overall, the study provides direct evidence for the potential of thimerosal to alter glutamate homeostasis in the central nervous system."

Mutkus and colleagues cite previous research by Mady Hornig et al. (see ARRI 18/2) showing that in genetically susceptible mice, thimerosal caused growth delay, reduced locomotion, and an exaggerated response to novel situations, as well as abnormal hippocampal neurons with altered glutamate receptors and transporters. They also note that their findings "corroborate previous studies by Aschner et al., Albrecht et al., and Brooks and Kristt, which showed that exposure to both inorganic and organic mercurials results in a significant decrease in glutamate uptake in primary cultures of rat and mouse cerebral cortical astrocytes."

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"In vitro uptake of glutamate in GLAST- and GLT-1-transfected mutant CHO-K1 cells is inhibited by the ethylmercury-containing preservative thimerosal," Lysette Mutkus, Judy L. Aschner, Tore Syversen, Gouri Shanker, Ursula Sonnewald, and Michael Aschner, *Biological Trace Element Research*, Vol. 105, 2005, 71-86. Address: Michael Aschner, Department of Physiology, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1083.

## Cough drug's effects point to glutamate dysregulation

Reporting a case study of a ten-year-old autistic boy who improved markedly when taking the over-the-counter cough medication dextromethorphan, Cooper Woodard and colleagues speculate that the drug's effects may stem from its glutamate-inhibiting mechanism.

The boy's parents, who initially gave their son dextromethorphan during an illness, noted that he improved greatly while taking the drug and regressed when it was stopped. Following up on their anecdotal report, the researchers monitored the child during a three-week course of dextromethorphan, using teacher and parent reports. They found that he became more cooperative, was less anxious, threw fewer tantrums, and showed more empathy toward others while taking the drug. When it was stopped, his behavior problems immediately escalated. Doctors had previously prescribed sertraline and citalopram to control the boy's behavior, but these drugs had produced no benefits.

The researchers say their findings are consistent with anecdotal reports of autistic or other developmentally children improving while taking dextromethorphan. They add, "Although it is difficult to rule out other factors that may have contributed to behavioral changes in a single case, there were no obvious changes in this child's situation that might account for the improvements noted and the reversal design helps to establish the apparent role the medication played."

Woodard et al. say that the boy's behavior changes in the second trial did not stem from improvements in illness-related symptoms, because by that time his acute illness had ended. While the drug does produce drowsiness, they say, a more likely explanation for its effects is that dextromethorphan acts as a glutamate receptor antagonist. Increasing evidence implicates dysregulation of glutamate, an excitatory neurotransmitter, as a factor in autism. (See related articles on this page.)

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"The treatment of the behavioral sequelae of autism with dextromethorphan: a case report," Cooper Woodard, June Groden, Matthew Goodwin, Cori Shanower, and Joanne Bianco, *Journal of Autism and Developmental Disorders*, Vol. 35, No. 4, August 2005, 515-8. Address: Cooper Woodard, The Groden Center, 86 Mount Hope Avenue, Providence, RI 02906, cwoodard@grodencenter.org.