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Discovery Points to Treatment Approach for Fragile X Syndrome

New research has found that many of the symptoms of fragile X syndrome, the most common cause of inherited mental retardation, can be eliminated in mice by reducing the expression of a single gene in the brain. The study suggests that the gene is a prime target for drugs to alleviate symptoms of the disorder, for which there is currently no specific treatment.

Howard Hughes Medical Institute investigator Mark Bear and his colleagues reported their findings in the December 20, 2007, issue of the journal *Neuron*. Gül Dölen, a member of Bear's laboratory at Massachusetts Institute of Technology, was the lead author of the research article. Bear and Dölen collaborated with researchers at Brown Medical School, India's National Institute of Mental Health and Neuroscience, and the Tata Institute of Fundamental Research in Bangalore, India.

Fragile X syndrome is the most common inherited form of mental retardation and is estimated to affect approximately 90,000 people in the United States. The condition is caused by a mutation in the *FMR1* gene on the X chromosome that prevents expression of a single protein, fragile X mental retardation protein (FMRP). The effects of fragile X vary between individuals, ranging from learning disability and hyperactivity to severe mental retardation. In addition to cognitive impairment and autistic behavior, children with fragile X can experience epileptic seizures and abnormal growth.

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- Mark F. Bear

The disorder is caused by loss of a functional version of FMRP. Bear and his colleagues suspected that FMRP might suppress protein synthesis in the brain and work in opposition to metabotropic glutamate receptor-5 (mGluR5), which turns on protein synthesis. "The theory was that when FMRP was

removed, protein synthesis was placed on a hair trigger, and that many pathologies of fragile X might be a consequence of that increase in protein synthesis,” he said. “The most exciting consequence of that theory was that it might be possible to correct fragile X by dialing back mGluR5 activation.”

To test this idea, the researchers knocked out one of the two copies of the gene for mGluR5 in mice that also lacked the gene for FMRP. The genetically engineered mice exhibited many of the symptoms observed in humans who have fragile X. By knocking out one copy of mGluR5, the researchers created mice that produced only half the normal amount of mGluR5 protein. And by cutting mGluR5 production in half, the researchers hoped that this would compensate for the lack of FMRP and eliminate the symptoms of fragile X.

“We decided to reduce the mGluR5 levels by 50 percent to reflect what might be a therapeutically relevant condition that would be achievable with carefully titrated drug treatment,” said Bear. “Total knockout of mGluR5 has deleterious effects, whereas reducing it by half is innocuous.”

The researchers found that reducing mGluR5 eliminated many of the symptoms of the disorder. Like humans with fragile X, mice without FMRP experience seizures, impaired memory, and accelerated body growth. When mGluR5 was diminished, these problems were corrected.

The reduction in mGluR5 also compensated for changes in the brain associated with increased protein synthesis. With less mGluR5, the brain of each mouse no longer formed an excessive number of neuronal connections. And the mice did not have a high density of dendritic spines that is characteristic of fragile X syndrome. Furthermore, the total rate of protein synthesis was reduced to normal levels in the brains of fragile X mice with reduced mGluR5.

The results of these experiments suggest drugs that block mGluR5 could prove to be the first effective treatment for fragile X syndrome, said Bear. Pharmaceutical companies have already developed a number of experimental drugs that block mGluR5, he said. Clinical trials are underway, but none of the drugs has yet been approved for humans. To speed drug development, Bear founded Seaside Therapeutics, a company that is now exploring the use of anti-mGluR5 drugs to treat fragile X syndrome.

Next on Bear's scientific agenda is an effort to determine which brain proteins are regulated by FMRP and mGluR5. Such information could help drug designers target pathologies of the disorder more precisely, he said. Bear and his colleagues are also exploring whether FMRP suppresses additional protein synthesis accelerators. These proteins might also make good targets for therapeutic drugs, Bear said.

Finally, he said, defects in the regulation of mGluR5 might also contribute to autism. “A picture is beginning to emerge that many single-gene disorders that cause autism might turn out to be genes that are similarly involved in the negative regulation of protein synthesis,” he said. “Thus, a significant fraction of cases of autism might be accounted for by excessive cerebral protein synthesis. If that were true, then mGluR5 antagonists might be therapeutically useful for much more than just fragile X.”