Fragile X retardation syndrome corrected in mice

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Researchers working with mice have significantly alleviated a wide range of abnormalities due to fragile X syndrome by altering only a single gene, countering the effects of the fragile X mutation. They said their achievement offers the potential for treatment of the disorder, the most common form of inherited mental retardation and a leading identified genetic cause of autism. There is currently no treatment or therapy for fragile X syndrome, whose symptoms include mental retardation, epilepsy, and abnormal body growth.

Mark Bear and colleagues reported their findings in an article in the December 20, 2007, issue of the journal *Neuron*, published by Cell Press.

Fragile X syndrome is known to be caused by loss of the gene for "fragile X mental retardation protein" (FMRP), which is believed to act as a brake on protein synthesis in specific areas of brain circuitry. The authors' idea was that loss of the "brake" would allow another protein that stimulates this process, called metabotropic glutamate receptor 5 (mGluR5), to function unchecked.

In their experiments to test this idea, the researchers studied mice that produce many of the characteristic pathologies of fragile X in humans due to a loss of the FMRP gene. The critical test, though, was when they also created double mutant mice that lacked both the FMRP gene and had a 50% reduction in mGluR5. They chose only to reduce the activity of the metabotropic glutamate receptor gene, rather than eliminate it, in

order to reflect what might be achieved using drug treatment for fragile X in humans.

Their tests on the double mutant mice revealed that the mGluR5 gene reduction greatly alleviated many abnormalities produced by loss of FMRP. The double mutant mice showed a rescue of abnormalities in brain structure and function, brain protein synthesis, memory, and body growth.

For example, loss of the FMRP gene produces overgrowth of the connections among neurons called dendritic spines. However, the additional 50% reduction in mGluR5 gene produced mice with completely normal spine density.

The double mutants also showed substantial reduction in epileptic seizures caused by lack of FMRP, found the researchers.

They concluded that “it is remarkable that by reducing mGluR5 gene dosage by 50%, we were able to bring multiple, widely varied fragile X phenotypes significantly closer to normal.”

They also concluded that “These findings have major therapeutic implications for fragile X syndrome and autism.”

Source: Cell Press

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