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Fragile X syndrome can be reversed in adult mouse brain

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A recent study finds that a new compound reverses many of the major symptoms associated with Fragile X syndrome (FXS), the most common form of inherited intellectual disability and a leading cause of autism. The paper, published by Cell Press in the April 12 issue of the journal *Neuron*, describes the exciting observation that the FXS correction can occur in adult mice, after the symptoms of the condition have already been established.

Fragile X patients suffer from a complex set of neuropsychiatric symptoms of varying severity which include anxiety, hyperactivity, learning and memory deficits, low IQ, social and communication deficits, and seizures. Previous research has suggested that inhibition of mGlu5, a subtype of receptor for the excitatory neurotransmitter glutamate, may be useful for ameliorating many of the major symptoms of the disease.

The new study, a collaboration between a group at F. Hoffmann-La Roche Ltd. in Switzerland, led by Dr. Lothar Lindemann, and a group at the Picower Institute for Learning at the Massachusetts Institute of Technology, led by Dr. Mark Bear, used a newly developed mGlu5 inhibitor called CTEP to examine whether pharmacologic inhibition of mGlu5 could reverse FXS symptoms.

The researchers used a mouse model of FXS and administered CTEP after the brain had matured. "We found that even when treatment with CTEP was started in adult mice, it reduced a wide range of FXS

symptoms, including learning and memory deficits and auditory hypersensitivity, as well as morphological changes and signaling abnormalities characteristic of the disease," reports Dr. Lindemann.

Although the CTEP drug itself is not being developed for humans, the findings have significance for human FXS. "The most important implications of our study are that many aspects of FXS are not caused by an irreversible disruption of brain development, and that correction of the altered glutamate signaling can provide widespread therapeutic benefit," explains Dr. Bear.

The researchers agree that future work may shed light on treatment of FXS in humans. "It will be of great interest to see whether treatment of FXS in human patients can be addressed in a similar broad fashion and with a similar magnitude as was suggested by our preclinical data," conclude Dr. Lindemann and Dr. Bear. "We anticipate that disturbed signaling can be corrected with other small molecule therapies targeting mGlu5 that are currently being used in human clinical trials."

More information: Michalon et al.: “Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice.” DOI:10.1016/j.neuron.2012.03.009

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