NEWS

Enzyme's discovery points to new approach for fragile X

BY **EMILY ANTHES**

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Researchers have discovered an enzyme that lowers brain levels of FMRP, the protein missing in people with **fragile X syndrome**. The findings, published 6 May in *Neuron*, suggest that blocking the enzyme could ease fragile X symptoms in people with the disorder who have low levels of FMRP and mild symptoms[1].

“You might be able to boost the levels of FMRP and hopefully ameliorate some of the symptomatology,” says lead researcher **Azad Bonni**, professor of neurobiology at Washington University in St. Louis. He notes, however, that the approach is unlikely to work for individuals with the full-blown syndrome who don’t make any FMRP.

Fragile X syndrome is a developmental disorder characterized by intellectual disability and often associated with autism. It is caused by mutations in a gene called **FMR1**, which encodes FMRP. People with the most severe mutations make no FMRP, whereas those with milder mutations produce low levels of the protein.

The new study focuses on an enzyme called CDH1-APC, which binds to certain proteins and flags them as waste. Previous studies have suggested that CDH1-APC also plays a role in synaptic plasticity — the process by which **synapses**, or neuronal connections, change in strength in response to experience.

In the new study, Bonni and his colleagues set out to learn more about the enzyme’s role in this neural process, which is thought to underlie learning.

The researchers engineered mice missing the enzyme and dissected the mice’s brains. They

isolated slices from the hippocampus — a brain structure involved in learning and memory — and exposed them to a chemical that causes synapses to weaken, quieting the communication between neurons.

In control mice, the researchers found, the connections did weaken. But in mice missing CDH1-APC, the synapses remained largely the same, suggesting the enzyme is necessary for them to change in this way.

Other research has revealed that the opposite occurs in mice missing FMRP: That is, synapses in the hippocampus weaken more than they do in controls in response to the chemical.

These opposing results led Bonni and his team to wonder whether FMRP is one of CDH1-APC's targets for destruction in the cell.

They found that the enzyme does bind to FMRP in brain tissue from normal mice, ultimately resulting in the degradation of the fragile X protein. In mice missing the enzyme, FMRP accumulates.

This accumulation of FMRP may impair synaptic plasticity: Prior research has suggested that FMRP inhibits the weakening of synapses, the researchers say.

The findings help to clarify the role of the fragile X protein in synaptic plasticity. "It's details like this that I think are important," says **Stephen Warren**, professor of human genetics at Emory University in Atlanta, who was not involved with the study.

The results also point to a new strategy for alleviating the cognitive and behavioral difficulties of some people with a mild form of fragile X. A drug that inhibits CDH1-APC, for example, may boost brain levels of FMRP in these individuals, improve their learning and ease their symptoms.

References:

1: Huang J. *et al. Neuron* **86**, 726-739 (2015) **PubMed**