Scientists find promise in intervention to normalize biological functions in Fragile X mice

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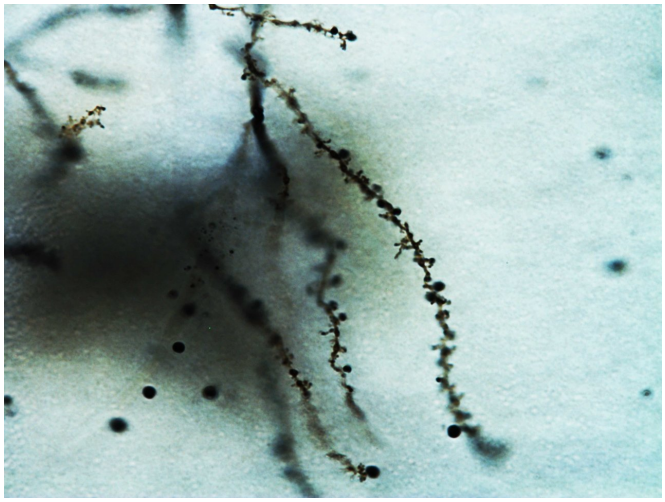

A team of neuroscientists has developed an intervention that normalizes multiple biological functions in mice afflicted with Fragile X Syndrome (FXS) -- including the structure of dendrites, a neuron component. Above is an abnormal dendrite of a neuron from FXS mice. Credit: Francesco Longo, NYU's Center for Neural Science.

A team of neuroscientists have developed an intervention that normalizes multiple biological functions in mice afflicted with Fragile X Syndrome (FXS). Its breakthrough centers on protein synthesis, or the building of proteins, and actin dynamics, which help regulate cellular processes—two functions that are inhibited in individuals with FXS.

"Our findings are consistent with the idea that an imbalance of protein synthesis and actin dynamics contribute to physiological problems in FXS mice," explains New York University Professor Eric Klann, director NYU's Center for Neural Science and the study's senior author. "Moreover, they offer a potential approach to treating individuals with Fragile X syndrome: targeting a specific protein, eIF4E, that regulates protein synthesis."

The findings, which appear in the journal *Science Signaling*, also included researchers from Belgium's Katholic University.

It's long been established that FXS is caused by silencing of the FMR1 gene, which is vital for cognitive development. This silencing leads to a loss in the expression of fragile X mental retardation protein (FMRP), which suppresses protein synthesis. Absent this suppressor, protein synthesis is exaggerated, producing a range of mental and physical disorders.

The lack of FMRP increases the functionality of eIF4E, which is required to initiate protein synthesis. Notably, it also disrupts the activity of a specific protein, CYFIP1, which regulates eIF4E as well as actin dynamics and the structure of dendrites—components of a neuron where inputs from other neurons are located.

In their work, the researchers utilized a drug, 4EGI-1, in order to reset the balance between protein synthesis and actin dynamics.

Specifically, the researchers treated FXS mice with 4EGI-1, which blocks interactions between eIF4E and a specific protein, eIF4G, a critical partner in initiating protein synthesis. This causes eIF4E to instead bind to CYFIP1, which reduces protein synthesis as well as a pathway that regulates actin dynamics.

Their results showed that this intervention was successful in normalizing both protein synthesis and actin dynamics. Moreover, this restoration also improved the model mice's synaptic function, diminished cognitive abnormalities, and normalized

the structure of dendrites.

More information: "Reducing eIF4E-eIF4G interactions restores the balance between protein synthesis and actin dynamics in fragile X syndrome model mice," *Science Signaling* (2017). stke.sciencemag.org/lookup/doi … 26/scisignal.aan0665

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