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Neuroscientists find promise in addressing Fragile X afflictions

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Neuroscientists at New York University have devised a method that has reduced several afflictions associated with Fragile X syndrome (FXS) in laboratory mice. Their findings, which are reported in the journal *Neuron*, offer new possibilities for addressing FXS, the leading inherited cause of autism and intellectual disability.

Those afflicted with FXS do not possess the protein FMRP, which is a suppressor of protein synthesis. Absent this suppressor, protein synthesis is exaggerated, producing a range of mental and physical disorders.

Previous research has indirectly targeted protein synthesis by seeking to temper, but not block, this process. The NYU researchers, by contrast, sought a more fundamental intervention—removing the enzyme, p70 ribosomal S6 kinase 1, or S6K1, which has previously been shown to regulate protein synthesis in FXS mice. By addressing this phenomenon at the molecular level, they hoped to diminish many of the conditions associated with FXS.

To determine the impact of this intervention, the researchers compared the behaviors of these FXS mice with those normal mice while also observing the physical attributes of these same FXS mice.

Their results showed that protein synthesis in the FXS mice lacking S6K1 became similar to that of normal mice. Moreover, through a series of experiments and other measurements (e.g., navigating a maze, interacting with other mice), they found both physical and behavioral

improvements in the FXS mice:

- The FXS mice missing the S6K1 enzyme showed greater ability than other FXS mice to adjust their behaviors when facing conditions that were similar, but not identical, to previous experiences. This attribute, behavioral flexibility, is typically diminished is those afflicted with FXS. In this experiment, the FXS mice missing the S6K1 enzyme were more successful than other FXS mice to navigate a maze that was similar to a maze they had previously mastered.
- The FXS mice missing the S6K1 enzyme showed enhanced social behaviors, which are measured through a commonly used "social novelty test." Under this method, mice interact with each other multiple times to gauge familiarity. In this experiment, the FXS mice missing the S6K1 enzyme showed greater familiarity with mice they previously encountered than did other FXS mice. Humans afflicted with FXS have diminished abilities for social interaction.
- The FXS mice missing the S6K1 enzyme showed a correction in three physical traits often associated with this condition: immature dendritic spine morphology, which indicates abnormal connections between neurons, excessive weight gain, and macro-orchidism, or enlarged testicles.

However, the researchers did not find uniform improvements in the tested FXS mice—they still engaged in excessive repetitive behaviors (i.e., repeatedly burying marbles in an experiment), a common trait among those afflicted with FXS.

Nonetheless, the research team said the findings showed remarkable promise.

"We think these results set the stage for a viable pharmacological approach to target S6K1, with the aim of diminishing or even reversing the afflictions associated with Fragile X syndrome," said Eric Klann, a professor in NYU's Center for Neural Science and the study's senior author.

Provided by New York University