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Neuroscientists find excessive protein synthesis linked to autistic-like behaviors

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Autistic-like behaviors can be partially remedied by normalizing excessive levels of protein synthesis in the brain, a team of researchers has found in a study of laboratory mice. The findings, which appear in the latest issue of *Nature*, provide a pathway to the creation of pharmaceuticals aimed at treating autism spectrum disorders (ASD) that are associated with diminished social interaction skills, impaired communication ability, and repetitive behaviors.

"The creation of a drug to address ASD will be difficult, but these findings offer a potential route to get there," said Eric Klann, a professor at NYU's Center for Neural Science and the study's senior author. "We have not only confirmed a common link for several such disorders, but also have raised the exciting possibility that the behavioral afflictions of those individuals with ASD can be addressed."

The study's other co-authors included researchers from the University of California, San Francisco (UCSF) and three French institutions: Aix-Marseille Universite'; Institut National de la Santé et de la Recherche Médicale (INSERM); and Le Centre National de la Recherche Scientifique (CNRS).

The researchers focused on the EIF4E gene, whose mutation is associated with autism. The mutation causing autism was proposed to increase levels of the eIF4E, the protein product of EIF4E, and lead to exaggerated protein synthesis. Excessive eIF4E signaling and exaggerated protein synthesis also may play a role in a range of

neurological disorders, including fragile X syndrome (FXS).

In their experiments, the researchers examined mice with increased levels of eIF4E. They found that these mice had exaggerated levels of protein synthesis in the brain and exhibited behaviors similar to those found in autistic individuals—repetitive behaviors, such as repeatedly burying marbles, diminished social interaction (the study monitored interactions with other mice), and behavioral inflexibility (the afflicted mice were unable to navigate mazes that had been slightly altered from ones they had previously solved). The researchers also found altered communication between neurons in brain regions linked to the abnormal behaviors.

To remedy to these autistic-like behaviors, the researchers then tested a drug, 4EGI-1, which diminishes protein synthesis induced by the increased levels of eIF4E. Through this drug, they hypothesized that they could return the afflicted mice's protein production to normal levels, and, with it, reverse autistic-like behaviors.

The subsequent experiments confirmed their hypotheses. The mice were less likely to engage in repetitive behaviors, more likely to interact with other mice, and were successful in navigating mazes that differed from those they previously solved, thereby showing enhanced behavioral flexibility. Additional investigation revealed that these changes were likely due to a reduction in protein production—the levels of newly synthesized proteins in the brains of these mice were similar to those of normal mice.

"These findings highlight an invaluable mouse model for autism in which many drugs that target eIF4E can be tested," added co-author Davide Ruggero, an associate professor at UCSF's School of Medicine and Department of Urology. "These include novel compounds that we are developing to target eIF4E hyperactivation in cancer that may also be

potentially therapeutic for autistic patients."

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