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Next-generation treatments for Fragile X syndrome

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A potential new therapeutic strategy for treating Fragile X syndrome is detailed in a new report appearing in the current issue of *Biological Psychiatry*, from researchers led by Dr. Lucia Ciranna at University of Catania in Italy.

Fragile X syndrome (FXS), the most common heritable form of autism and intellectual disability, is one of the most exciting areas in brain research at the moment.

A decade ago, Dr. Mark Bear and his colleagues discovered that an animal model for FXS was associated with a distinctive alteration in brain function, enhanced long-term depression, which was mediated by a specific mechanism, enhanced signaling via the metabotropic glutamate receptor 5 (mGluR5). Dr. Bear and his colleagues proceeded to show that blocking mGluR5 showed promise in animal models as the first treatment for FXS. A recent preliminary study of the drug fenobam, an mGluR5 blocker, provided hints of some beneficial effects in adults with FXS.

mGluR5 blockers are likely to be the first examples of several therapeutic mechanisms that will emerge in upcoming years. Now, Ciranna and colleagues have identified another potential therapeutic mechanism for FXS.

Using a mouse model of FXS, they demonstrate that blockade of the serotonin 7 (5-HT7) receptor, like mGluR5 blockade, reduces long-term

depression mediated by mGlu receptors. In neuroscience, long-term depression is the term used to describe a reduction or decrease in the effectiveness of neuronal synapses, meaning that the ability of nerve cells to communicate is diminished.

The effect that they detected occurred in the hippocampus, one of the brain structures most crucially involved in learning and memory.

"This result opens new perspectives in the therapy of Fragile X Syndrome, suggesting that selective agonists for 5-HT7 receptors might become useful pharmacological tools," said Ciranna.

This led them to study the effects of LP-211, a new compound with a high affinity and selectivity for 5-HT7 receptors. The data showed that LP-211 behaves as an agonist of 5-HT7 receptors and therefore, may be used as a potential treatment for Fragile X syndrome, although much more work would be necessary before it could be tested in humans.

"This study illustrates a critical issue in the development of new treatments for psychiatric disorders. It is uncommon that all patients with a particular disorder will tolerate or respond to a single treatment. Thus, we need multiple approaches to treatment," commented Dr. John Krystal, Editor of Biological Psychiatry. "Further, this study illustrates how a single insight into the biology of an illness, in this case enhanced mGluR5 signaling, yields multiple novel mechanisms that might be explored to develop novel treatments."

More information: The article is "Activation of 5-HT7 Serotonin Receptors Reverses Metabotropic Glutamate Receptor-Mediated Synaptic Plasticity in Wild-Type and Fmr1 Knockout Mice, a Model of Fragile X Syndrome" by Lara Costa, Michela Spatuzza, Simona D'Antoni, Carmela M. Bonaccorso, Chiara Trovato, Sebastiano A. Musumeci, Marcello Leopoldo, Enza Lacivita, Maria V. Catania, and

Lucia Ciranna (doi: 10.1016/j.biopsych.2012.06.008). The article appears in *Biological Psychiatry*, Volume 72, Issue 11 (December 1, 2012).