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

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Background: Fragile X syndrome (FXS) is a genetic cause of intellectual disability and autism. Fmr1 knockout (Fmr1 KO) mice, an animal model of FXS, exhibit spatial memory impairment and synapse malfunctioning in the hippocampus, with abnormal enhancement of long-term depression mediated by metabotropic glutamate receptors (mGluR-LTD). The neurotransmitter serotonin (5-HT) modulates hippocampal-dependent learning through serotonin 1A (5-HT1A) and serotonin 7 (5-HT7) receptors; the underlying mechanisms are unknown.

Methods: We used electrophysiology to test the effects of 5-HT on mGluR-LTD in wild-type and Fmr1 KO mice and immunocytochemistry and biotinylation assay to study related changes of 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA) glutamate receptor surface expression.

Results: Application of 5-HT or 8-OH-DPAT (a mixed 5-HT1A/5-HT7 agonist) reversed mGluR-LTD in hippocampal slices. Reversal of mGluR-LTD by 8-OH-DPAT persisted in the presence of the 5-HT1A receptor antagonist WAY-100635, was abolished by SB-269970 (5-HT7 receptor antagonist), and was mimicked by LP-211, a novel selective 5-HT7 receptor agonist. Consistently, 8-OH-DPAT decreased mGluR-mediated reduction of AMPA glutamate receptor 2 (GluR2) subunit surface expression in hippocampal slices and cultured hippocampal neurons, an effect mimicked by LP-211 and blocked by SB-269970. In Fmr1 KO mice, mGluR-LTD was abnormally enhanced; similarly to wild-type, 8-OH-DPAT reversed mGluR-LTD and decreased mGluR-induced reduction of surface AMPA receptors, an effect antagonized by SB-269970.

Conclusions: Serotonin 7 receptor activation reverses metabotropic glutamate receptor-induced AMPA receptor internalization and LTD both in wild-type and in Fmr1 KO mice, correcting excessive mGluR-LTD. Therefore, selective activation of 5-HT7 receptors may represent a novel strategy in the therapy of FXS.