P4.03.

The Fragile Nature of Endocannabinoid Signalling in Fragile X Syndrome

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Fragile X Syndrome (FXS) is the most common form of inherited mental retardation and is caused by genetic silencing of the fmr1 gene, resulting in loss of the fragile X mental retardation protein (FMRP). The "mGlu-Theory" of FXS states that enhanced group I metabotropic glutamate receptor (mGlu) activity may explain the phenotypic manifestation of FXS. Glutamatergic synapses in the nucleus accumbens express a form of long term depression (LTD) requiring endocannabinoid (eCB) production via activation of postsynaptic mGlu5 receptors and their coupling to diacylglycerol lipase-α (DGL-α). To our surprise, this form of synaptic plasticity was completely missing in FMRP-KO mice. Neither basal eCB levels nor CB1 receptor function was changed, but a significant decrease in mGlu5-induced DGL-α activity was observed in FMRP-KO mice suggesting that FMRP loss resulted in a functional uncoupling of mGlu5 from DGL-α. To test this hypothesis, we performed a detailed electron microscopy study, which revealed that DGL-α distribution was concentrated perisynaptically at glutamatergic synapses in wild type, but not in FMRP-KO mice. Instead, the levels of DGL-α within the spine head cytoplasm were significantly higher in FMRP-KO animals. Similar biased perisynaptic distribution of mGlu5 was found in both groups. Thus, we conclude that absence of FMRP results in loss of eCB-LTD in the nucleus accumbens, which may be explained by functional uncoupling of mGlu5 and DGL-α at glutamatergic synapses.