Pharmacological investigation into the mechanisms underlying altered mGlu5 receptor dynamics in a mouse model of Fragile X Syndrome

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Altered metabotropic glutamate receptor subunit 5 (mGluR5) function is strongly implicated in the pathophysiology of Fragile X Syndrome (FXS), a leading inherited cause of intellectual disability and autism. The precise mechanisms underlying the defective mGluR5 signalling are not known and despite the prominent role of mGluR5 in the regulation of synaptic plasticity and cognitive functions very little is known about its trafficking and dynamics at the synapse.
Previously, we have shown that in the animal model of FXS, the *Fmr1* knockout (*Fmr1* KO) mouse, mGluR5 is less associated with Homer proteins, which are post-synaptic density (PSD) partners of mGluR5. In this study we asked now the question what the consequence of this disrupted mGluR5/Homer crosslink is for the surface expression and spine membrane trafficking of these receptors. To achieve this we used a powerful combination of novel live-cell single molecule tracking together with immunocytochemical and biotinylation approaches in cultured hippocampal neurons from *Fmr1* KO and littermate wild-type (WT) control mice.
We show that the lateral mobility of mGluR5 is increased within the synapse but not at the extrasynaptic sites in neurons of *Fmr1* KO mice as compared to WT mice. In agreement with our prediction, disrupting the mGluR5/Homer crosslink in WT mice with a specific peptide mimics the *Fmr1* KO phenotype by inducing a similar rate of mGluR5 surface diffusion. Despite their increased mobility in *Fmr1* KO neurons, mGluR5s seem to be spatially more confined in their exploratory behaviour. This could be due to a steric hindrance within the membrane related to an excessive mGluR5-dependent protein synthesis and thus increased expression of membrane proteins in the disease state. Pre-treatment with the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (i.e. MPEP) indeed rescues this phenotype to almost WT level.
In summary, our findings demonstrate an alteration of the mGluR5 dynamics in the synaptic membrane of Fmr1 KO hippocampal neurons and provide a new cellular mechanism for the mGluR5 dependent pathophysiology in FXS.