Fragile X syndrome and neuronal deficits

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Lack of fragile X mental retardation protein (FMRP) causes fragile X syndrome, a common form of inherited mental retardation. FMRP is an RNA binding protein and is thought to be involved in translation efficacy and/or trafficking of certain mRNAs. Recently, a subset of mRNAs has been identified to which FMRP is binding with high affinity. These FMRP-associated mRNAs contain an intramolecular G quartet structure.
In neurons, dendritic mRNAs are involved in local synthesis of proteins in response to synaptic activity and this represents a mechanism for synaptic plasticity. We have generated an FMR1-EGFP stable transfected PC12 cell line with an inducible expression system (Tet-On) for regulated expression of the FMRP-GFP fusion protein. After Dox-induction, FMRP-GFP was localized in granules in the neurites of PC12 cells. Using time lapse microscopy, the trafficking of FMRP-GFP granules was demonstrated into the neurites of living PC12 cells. Motile FMRP-GFP granules displayed two types of movements: oscillatory (bi-directional) and unidirectional anterograde. The average velocity of the granules was 0.19 µm/sec with a maximum speed of 0.71 µm/sec. In addition, we showed that the movement of FMRP-GFP labeled granules into the neurites was microtubule dependent.
The transported mRNA products play a role in the maturation of the spine as Fmr1 KO mice show immature spines. In the spines FMRP is controlling the translation of mRNAs giving the option of a quick response after signalling. If FMRP is missing there is no control as can be seen by the lack of control of expression of Map1B in the dendrites.
One of the consequences of the absence of FMRP in Purkinje cells of Fmr1 null-mutants is the enhanced LTD induction at the parallel fiber synapses that innervate these spines. The mutants show impaired cerebellar delay eyeblink conditioning in that the percentage of conditioned responses as well as their peak amplitude and velocity are reduced.

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