

## Abstract 19

### THE GABA(A) RECEPTOR AS A POTENTIAL TARGET FOR THERAPY OF THE FRAGILE X SYNDROME

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The fragile X syndrome is a common form of inherited mental retardation. Patients suffer from mild to severe cognitive impairment, recognizable facial features, behavioural abnormalities and an increased rate of spontaneous epilepsy. A mouse model has been developed that mimics the cognitive and clinical symptoms of the disorder. FMRP, the RNA-binding protein missing in fragile X syndrome, regulates mRNA localization to dendrites as well as mRNA translation and so influences local protein synthesis. Previously we have shown that a dysfunction of the GABAergic system is involved in the clinical presentation of the disorder. We demonstrated a 35-50% reduced expression of 8 of the 18 subunits that make up the GABA receptor and of enzymes involved in GABA synthesis (GAD), transport (GAT1 and GAT44) and degradation (SSADH). A reduction of corresponding genes was observed in the fragile X fly model, indicating decreased GABAergic expression is an evolutionary conserved hallmark of the fragile X syndrome. We demonstrated that FMRP binds several components of the GABAergic system resulting in an apparent increase in stability of these mRNA transcripts. In addition, we show that the previously reported under expression of specific subunits of the GABA(A) receptor can be corrected in a YAC transgenic mouse model, containing the full length human FMR1 gene in a knockout background. These results suggest that under expression of the GABA(A) receptor is a result of a direct interaction of FMRP with the encoding mRNAs. We argue that the malfunction of the GABAergic system underlies many of the clinical symptoms of fragile X patients. Despite the altered composition of the GABA(A) receptor in the fragile X syndrome, rotarod and elevated plus maze experiments in mice showed that these are still functional. We postulate that the well described GABA(A) receptor pharmacology might open new powerful opportunities for treatment of the behavioural and epileptic phenotype associated with fragile X syndrome.