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Invited review

The role of fragile X mental retardation protein in major mental disorders

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ABSTRACT

Fragile X mental retardation protein (FMRP) is highly enriched in neurons and binds to approximately 4% of mRNAs in mammalian brain. Its loss is a hallmark of fragile X syndrome (FXS), the most common form of mental retardation. In this review we discuss the mutation in the fragile X mental retardation-1 gene (FMR1), that leads to FXS, the role FMRP plays in neuronal cells, experiments from our own laboratory that demonstrate reductions of FMRP in additional psychiatric disorders (autism, schizophrenia, bipolar disorder, and major depressive disorder), and potential therapies to ameliorate the loss of FMRP.

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1. Fragile X syndrome and the fragile X mental retardation gene

Fragile X syndrome (FXS), is the most common inherited form of mental retardation which affects approximately 1:4500 males and 1:9000 females (Huber, 2006). Subjects with FXS display learning difficulties, delayed language acquisition, impairment of fine motor skills, and behavioral deficits reminiscent of autism including repetitive behavior, decreased attention, and poor eye contact (Hagerman, 1996). Seizures are another common feature of FXS, affecting approximately 20% of patients (Partington, 1984). More than 80% of males with FXS also display macroorchidism (Bardoni et al., 2001). All cases of FXS are the result of an abnormality of the fragile X mental retardation-1 gene.

The fragile X mental retardation-1 (FMR1) gene is located to the X chromosome and mutations in this gene are almost entirely responsible for the development of FXS. The gene was first identified in 1991 (Verkerk et al., 1991). FXS is caused by an expansion of a CGG repeat in the 5′ untranslated portion of the gene. In the normal form of the gene there are anywhere from 5 to 55 CGG repeats (Fu et al., 1991). Individuals with between 56 and 200 repeat premutations of the gene, which lack methylation, do not display obvious clinical symptoms of FXS but are found in FXS families (Bardoni et al., 2001). However, in individuals with the full mutation of over 200 repeats, there is extensive methylation, including the CpG islands in the gene's promoter region, resulting in transcriptional silencing of the gene (Pieretti et al., 1991). Expansion from premutation to the full mutation occurs only during maternal transmission (Oostra and Willemsen, 2009). These individuals do not produce the gene product, fragile X mental retardation protein (FMRP) and display the clinical symptoms of FXS.

Carriers of the premutation are at risk for developing a separate disorder called Fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is a progressive neurodegenerative disorder characterized by action tremor and ataxia. Advanced or severe cases also display cognitive decline (Hagerman and Hagerman, 2007). More than one third of premutation carriers over age 50 display symptoms of FXTAS, and by age 70 more than 50% of male carriers show FXTAS (Jacquemont et al., 2004).

2. Fragile X mental retardation protein

FMRP is an RNA binding protein that is highly expressed in neurons (Devys et al., 1993) and glial cells (Pacey and Doering, 2007) and functions primarily as a regulator of translation. FMRP contains both nuclear localization and export domains allowing it to move between the nucleus and the cytoplasm (Eberhart et al., 1996; Sittler et al., 1996). However, in neurons, the vast majority of FMRP is

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localized to the cytoplasm with primary sublocalization to the dendrites, spines, and soma (Bakker et al., 2000; Weiler et al., 1997). FMRP associates, in an mRNA dependent manner, with large polyribosome complexes (Ceman et al., 1999; Feng et al., 1997; Willemsen et al., 1996) and smaller mRNA ribonucleoprotein complexes (mRNP), and dendritic "RNA granules" which are complexes of ribosomes, RNA binding proteins, and RNAs. The RNA granules travel on microtubules to the dendrites and are believed to be translationally arrested (Antar et al., 2005; Kanai et al., 2004). Antar et al. (2004) demonstrated that mGluR5 activation increased the presence of FMRP to dendrites of cultured hippocampal neurons, and this increase was not due to increased synthesis of mRNA. A further study (Antar et al., 2005) showed that FMRP-associated RNA granules also increased in the dendrites in response to glutamatergic signaling and that this increase was reduced if microtubule dynamics were disrupted.

FMRP has been shown to bind approximately 4% of mRNA expressed in mammalian brain including its own message (Bassell and Warren, 2008). Specific mRNA targets of FMRP or other components of the RNP include myelin basic protein (MBP); microtubule-associated protein 1B (MAP1B), calcium/calmodulin protein kinase II alpha (CAMK2A), activity-regulated cytoskeletal-associated protein (ARC), ras related C3 botulinum toxin substrate 1 (RAC1), AMAP receptor subunits GluR1 and GluR2, and SAP90/PSD-95-associated protein 4 (SAPAP4) (Brown et al., 1998,2000, 2001; Castets et al., 2005; Hou et al., 2006; Muddashetty et al., 2007; Zalfa et al., 2003). At the dendrites, FMRP may have a primary function as a transcriptional repressor. In the dendrites of Fmr1 knockout (KO) mice, there is increased protein synthesis for a number of proteins including PSD-95, Arc, and GluR1 (Hou et al., 2006; Muddashetty et al., 2007; Zalfa et al., 2007).

Microarray experiments also have identified genes that display altered expression in the absence of FMRP. In a study using lymphoblastoid cell lines from males with Fragile X syndrome there were 90 genes that showed significantly altered expression of at least 1.5 fold (Bittel et al., 2007). Quantitative real time polymerase chain reaction (qRT-PCR) confirmed altered expression of a number of genes including MAP1B, gamma-aminobutyric acid receptor subunit delta (GABRδ), and unc-13 homolog B (UNC13B) (Bittel et al., 2007). UNC13B is a presynaptic protein that interacts with syntaxin 1 and 2 to promote priming of synaptic vesicles (Betz et al., 1997; Richmond et al., 2001). MAP1B codes for a precursor protein that undergoes proteolytic cleavage to form the MAP1B heavy chain and L1 light chains (Hammarback et al., 1991). As microtubule assembly is an important step in neurogenesis, impairment of MAP1B expression may affect normal brain development and neuronal plasticity. The GABRδ subunit, combines with other $GABA_A$ receptor subunits to form a ligand-gated chloride channel (Windpassinger et al., 2002). Interestingly, GABRδ mRNA has also been shown to be downregulated in hippocampus and neocortex of Fmr1 KO mice (Gantois et al., 2006). Other $GABA_A$ receptor subunits have been shown to display reduced expression in animal models of FXS including GABRα1, GABRα4, GABRβ1, GABRβ2, GABRγ1, and GABRγ2 (D'Hulst et al., 2006; El Idrissi et al., 2005). As GABA is the main inhibitory neurotransmitter in brain, disruption of GABA signaling could possibly explain seizures that are often comorbid with FXS.

3. FMRP is reduced in brains of subjects with autism

As previously mentioned, there are behavioral deficits in common between subjects with autism and subjects with FXS. Moreover, up to 30% of subjects with FXS are comorbid for autism while 2–3% of subjects with autism display comorbid FXS (Kau et al., 2004; Hagerman et al., 2005). Our laboratory was interested in investigating whether subjects with autism also displayed reductions in FMRP. We examined FMRP protein expression in two brain regions: cerebellar vermis and superior frontal cortex [Brodmann's Area 9 (BA9)], two regions that show extensive pathology in subjects with autism (Bauman and Kemper, 1994,2005). For all experiments, FMRP was normalized against both neuronal specific enolase (NSE) and β-actin in order to ensure that the observed changes were specific for FMRP. In cerebellar vermis of adult subjects with autism, there was a significant reduction in levels of FMRP when compared with matched controls (Fig. 1A; Fatemi et al., in press). In contrast there was no significant difference in FMRP levels in vermis between children with autism and matched child controls (Fig. 1A; Fatemi et al., in press). In BA9 of adults, there was also a significant reduction in FMRP protein expression (Fatemi, unpublished observations). As with cerebellar vermis, there was no change in FMRP expression in BA9 of children with autism (Fatemi, unpublished results).

In addition to FMRP, we also investigated protein levels of metabotropic glutamate receptor 5 (mGluR5) and gamma-aminobutyric acid (GABA) A receptor, beta 3 (GABRβ3) in both vermis and BA9. Activation of group 1 metabotropic glutamate receptors (including mGluR5) result in increased synthesis of synaptic proteins (Weiler and Greenough, 1993). In the absence of FMRP, processes that depend upon protein synthesis such as epileptiform discharges (Chuang et al., 2005) and improper regulation of long term depression (Hou et al., 2006) are enhanced, suggesting that protein synthesis resulting from mGluR-stimulation is inhibited by FMRP. In animal models of FXS, inhibitors of mGluR5 have been shown to rescue several FXS phenotypes (de Vrij et al., 2008; Yan et al., 2005) as does reduction in mGluR5 expression (Dölen et al., 2007). However, expression of mGluR5 does not appear to be altered in Fmr1 KO mice (Price et al., 2007; Zhang and Alger, 2010). A recent study found that there was no change in mGluR1, mGluR5, or endocannabinoid receptor expression in hippocampi of Fmr1 KO mice when compared with wild type (Zhang and Alger, 2010). Price et al. (2007) also found

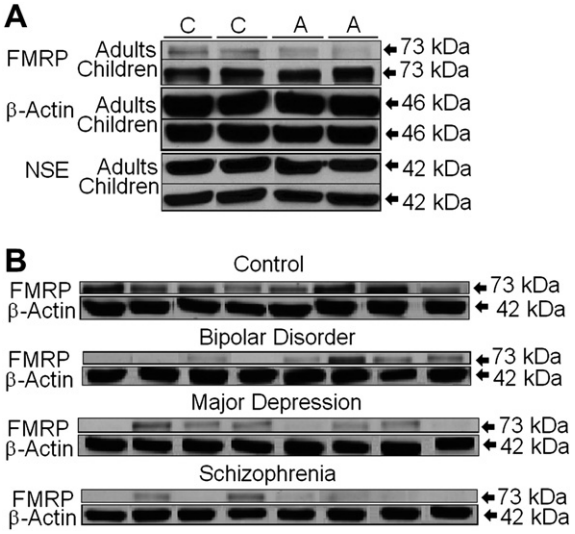

Fig. 1. Reduction of FMRP is subjects with autism (A), and subjects with bipolar disorder, major depression, and schizophrenia (B) vs. controls. **A:** Expression of FMRP, β-actin, and neuronal specific enolase (NSE) in cerebellar vermis from subjects with autism (A) and control subjects (C). **B:** Expression of FMRP and β-actin in lateral cerebellum of subjects with bipolar disorder, major depression, and schizophrenia. Part A reprinted from Anatomical Record (In press, 2011), Fatemi, S.H., Folsom, T.D., Kneeland, R.E., Liesch, S.B., Metabotropic glutamate receptor 5 upregulation in children with autism is associated with underexpression of both Fragile X mental retardation protein and $GABA_A$ receptor beta 3 in adults with autism, Figs. 1 and 2 Copyright (2010), with permission from John Wiley and Sons. Part B reprinted from Schizophrenia Research, 124(1–3):246–247, Fatemi, S.H., Kneeland, R.E., Liesch, S.B., Folsom, T.D., Fragile X mental retardation protein levels are decreased in major psychiatric disorders, page 247, Fig. 1, Copyright (2010), with permission from Elsevier.

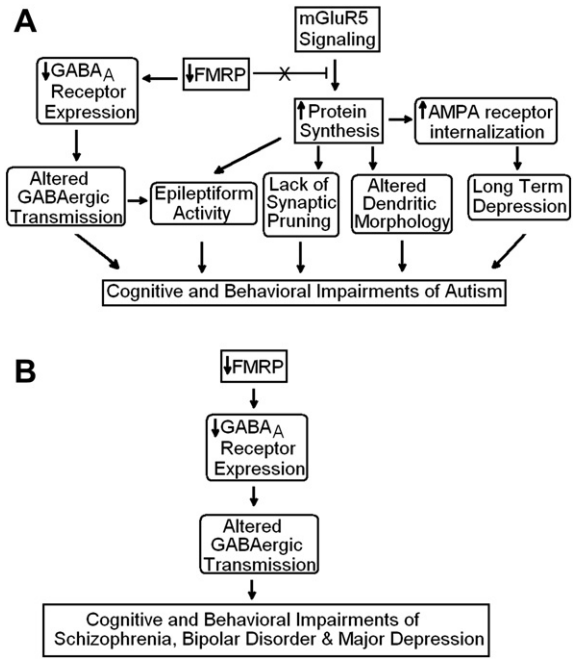

Fig. 2. The effects of reduced FMRP in major mental disorders. Evidence from animal studies suggests that a reduction in FMRP leads to a reduction in a number of $GABA_A$ receptor subunits. This reduction could potentially lead to altered GABAergic transmission and GABA/glutamate balance in the brain potentially explaining increased seizure and cognitive disturbances of subjects with FXS and other psychiatric disorders. FMRP normally acts as an inhibitor of protein synthesis resulting from mGluR5 activation. In the absence of FMRP there is increased protein synthesis. The increased protein synthesis results in increased internalization of AMPA receptors ultimately leading to long term depression. Moreover, increased protein synthesis may be responsible for altered morphology of dendrites, epileptiform activity, and lack of synaptic pruning in autism (A) or altered GABA transmission and subsequent deficits in cognition in schizophrenia, bipolar disorder and major depression (B).

that in spinal cord of Fmr1 KO mice there was no difference in mGluR5 expression compared with wild type. These studies suggest that mGluR5 activation may be independent of FMRP action, at least in Fmr1 KO mice.

$GABA_A$ receptors are also known to be targets of FMRP as animal models for FXS have shown reduction in multiple $GABA_A$ receptor subunits (Fig. 2; D'Hulst et al., 2006; El Idrissi et al., 2005; Gantois et al., 2006). mGluR5 was measured as a dimer (224 kDa) and total protein (dimer plus 112 kDa monomer). In vermis of children with autism there was a significant increase in mGluR5 dimer and total mGluR5 protein when compared with healthy controls (Fatemi et al., in press). Similarly, in BA9, we also observed significant increases in mGluR5 dimer and total mGluR5 in children with autism (Fatemi, unpublished results). Interestingly, in vermis of children with autism there was an increase in the ratio of dimerized mGluR5 to total mGluR5 (Fatemi et al., in press) There were no significant differences in mGluR5 protein in BA9 and vermis of adults with autism vs. control subjects. Finally, in vermis, but not BA9, we observed a significant reduction in protein for GABRβ3 when compared with controls (Fatemi et al., in press). These results persuaded us to look for potential involvement of FMRP in other psychiatric disorders. Thus, we pursued measuring levels of FMRP in three other disorders: schizophrenia, bipolar disorder, and major depressive disorder.

4. FMRP is reduced in lateral cerebellum in subjects with schizophrenia and mood disorders

Studies examining the FMR1 gene and a possible association with schizophrenia have found that mutations in the FMR1 gene do not seem to confer a greater risk for the development of schizophrenia (Ashworth et al., 1996; Jnsson et al., 1995). However, a small number of case reports have identified individuals who display psychosis also have FMR1 mutations (Ashworth et al., 1996; Jnsson et al., 1995; Khin et al., 1998). Thus far, there have been no findings showing an association between FMR1 and either bipolar disorder or major depressive disorder (MDD).

Our laboratory studied protein levels of FMRP in lateral cerebella of subjects with schizophrenia, bipolar disorder, and MDD, and healthy controls from the Stanley Neuropathology Consortium. As with our studies with subjects with autism, all FMRP measurements were normalized against β-actin. Analysis of variance (ANOVA) showed a significant difference between the four means (Fatemi et al., 2010). Individual comparisons were subsequently made and we observed significant reductions in FMRP in subjects with schizophrenia, bipolar disorder, and MDD when compared with controls (Fig. 1B; Fatemi et al., 2010). These changes were specific for FMRP as there were no significant differences in expression of β-actin (Fig. 1B). Moreover, analysis of confounding variables found that none of them had an impact on FMRP expression (Fatemi et al., 2010).

5. Implications for involvement of FMRP in psychiatric disease

Our laboratory found reductions in FMRP in autism, schizophrenia, bipolar disorder, and MDD. These results are significant as they are the first to demonstrate that FMRP is reduced in brains of subjects that have not been diagnosed with FXS. Cognitive deficits are common to members of these four diagnostic groups and GABAergic dysfunction is likely to contribute to these deficits. Fmr1 knockout mice and *Drosophila* display reduced expression of $GABA_A$ receptors (D'Hulst et al., 2006; El Idrissi et al., 2005; Gantois et al., 2006). Reduced FMRP expression in subjects with autism, bipolar disorder, schizophrenia and MDD could potentially explain the observed reductions of $GABA_A$ and $GABA_B$ receptor expression in postmortem brain studies performed by our laboratory (Fatemi et al., 2009a,b, 2010, unpublished observations). GABAergic dysfunction in these four disorders has been demonstrated in postmortem studies by altered expression mRNA and protein of glutamic acid decarboxylase 65 and 67 kDa (GAD65/67) (Akbarian et al., 1995; Fatemi et al., 2002, 2005; Guidotti et al., 2000; Yip et al., 2007, 2008), and $GABA_A$ and $GABA_B$ receptors (Blatt, 2005; Duncan et al., 2010; Fatemi et al., 2009a,b, 2010, unpublished observations; Oblak et al., 2010, in press; Ghose et al., 2011). Presence of seizure disorder in subjects with autism (as well as those with FXS) may also contribute to cognitive dysfunction. However, aside from individuals in our population sample diagnosed with autism, none of the subjects diagnosed with bipolar disorder, schizophrenia, or major depression were comorbid for seizure disorder.

Glutamatergic signaling is also affected by loss of FMRP. Stimulation of group 1 metabotropic glutamate receptors (mGluR) results in signaling cascades post-synaptically, causing increased protein synthesis (Weiler and Greenough, 1993, 1999). In contrast, there is evidence that FMRP acts as a negative regulator of protein synthesis (Dölen et al., 2007). Multiple phenomena observed in Fmr1 KO mice including long term depression, increased density of long, thin dendritic spines, and epileptiform activity are dependent on both mGluR activity and protein synthesis (Dölen and Bear, 2008). It has been hypothesized that reduction in FMRP expression leads to unregulated protein synthesis induced by group 1 mGluRs, which in turn is responsible for the multiple physical and cognitive pathologies of FXS (Fig. 2; Bear et al., 2004; Dölen and Bear, 2008).

Table 1
Summary of agents that are capable of ameliorating effects of unchecked mGluR5 signaling.

Agent	Mode of action	Animal	Effect	Reference
MPEP	mGluR5 inhibitor	Mouse	Correction of PPI	de Vrij et al., 2008
			Reduction of dendritic protrusions	de Vrij et al., 2008
			Repression of seizures	Westmark et al., 2009
			Rescue of open field behavior	Yan et al., 2005
			Rescue of repetitive self-grooming behavior	Silverman et al., 2010
Lithium	Mood stabilizer	Mouse	Rescue of open field behavior	Yuskaitis et al., 2010
		Human	Corrected behavioral deficits in subjects with FXS	Berry-Kravis et al., 2008
Fenobam	mGluR5 inhibitor	Human	Correction of PPI	Berry-Kravis et al., 2009

The reduced expression of FMRP may also have consequences for synaptic plasticity. A consistent feature in both subjects with FXS and Fmr1 KO mice is the presence of dendrites with abundance of long, thin spines which suggest an immature morphology (Fig. 2; Grossman et al., 2006; Irwin et al., 2002; Meredith et al., 2007). Interestingly, Vanderklish and Edelman (2002) found that stimulation of group 1 mGluRs of cultured hippocampal neurons resulted in increased length of dendritic spines, further supporting the role of glutamatergic signaling in the pathology of FXS. The increased number of long, thin dendritic spines could potentially result in an abnormally large number of synapses. The large number of synapses may result in cognitive impairments associated with FXS as well as autism. Animal models have provided evidence that FMRP may play a role in synaptic pruning (Fig. 2; Pfeiffer and Huber, 2007; Tessier and Broadie, 2008). Tessier and Broadie (2008) found that *Drosophila* FMRP (dFMRP) is required for axonal pruning of the mushroom body, the primary learning and memory region of *Drosophila* brain. Similarly, Pfeiffer and Huber (2007) found that overexpression of FMRP in neurons cultured from Fmr1 KO mice resulted in a reduction of synapse number.

6. Potential avenues for treatment

In support of the mGluR theory of FXS, animal experiments have shown that structural and behavioral deficits associated with FXS and presence of seizure can be ameliorated or rescued through the use of lithium and the mGluR5 antagonist MPEP (2-methyl-6-(phenylethynyl)-pyridine) or by reducing levels of mGluR5 (de Vrij et al., 2008; Dölen et al., 2007;Westmark et al., 2009; Yan et al., 2005; Yuskaitis et al., 2010). de Vrij et al. (2008) found that treatment with MPEP rescued prepulse inhibition (PPI) of the acoustic startle response in Fmr1 KO mice and reduced the number of dendritic protrusions from cultured hippocampal neurons. MPEP has also been shown to repress seizures in Fmr1 KO mice (Westmark et al., 2009; Yan et al., 2005). Additionally Yan et al. (2005) found that treatment with MPEP reduced center field behavior in the open field test, demonstrating that MPEP could also affect behavioral phenotypes. Dölen et al. (2007) generated Fmr1 KO mice that express 50% as much mGluR5 and found that a number of phenotypes associated with FXS which are common to Fmr1 KO mice were rescued including a reduction in density of dendritic spines of pyramidal cells from the visual cortex and reduced presence of audiogenic seizures. Interestingly, the reduction in mGluR5 also resulted in reduced protein synthesis in the hippocampus (Dölen et al., 2007). Finally, chronic treatment with lithium has been shown to rescue behaviors that are altered in Fmr1 KO mice including open field behavior and passive avoidance (Yuskaitis et al., 2010). These results, taken together, suggest that drugs that affect mGluR5 signaling may serve as potential therapies for treatment of FXS. Recently, MPEP has been shown to reduce repetitive self-grooming in a mouse model of autism (Silverman et al., 2010).

A recent study has shown that treatment with lithium resulted in behavioral improvements in subjects with FXS including improved scores on the Aberrant Behavior Checklist-Community Edition, clinical global improvement scale, and the Vineland Adaptive Behavior Scale (Berry-Kravis et al., 2008). An open label pilot study using a single dose of fenobam, a selective, potent mGluR5 inhibitor (Porter et al., 2005), in adults with FXS found a 20% improvement over baseline for PPI (Berry-Kravis et al., 2009). Moreover, no significant adverse effects of fenobam on the study subjects were identified (Berry-Kravis et al., 2009). Table 1 summarizes the use of chemical agents that remedy the effects of unchecked mGluR5 signaling. Further studies are required to determine the efficacy and safety of mGluR inhibitors to correct for deficits caused by reduction or absence of FMRP in subjects with major mental disorders.

7. Conclusions

FXS is the most common form of mental retardation which is caused by an expansion of a CGG repeat in the 5′ untranslated portion of the FMR1 gene. This expansion results in hypermethylation of the FMR1 promoter and consequent loss of its protein product FMRP. Our laboratory has demonstrated for the first time that reduction in FMRP in brain tissue is not specific to FXS but occurs in patients with autism, schizophrenia, bipolar disorder, and major depression. Evidence from animal models suggests that the loss of FMRP and resultant increase in mGluR signaling and protein synthesis may be responsible for the observed pathologies of FXS. The use of mGluR inhibitors may prove to be a safe, effective way in the treatment of FXS and other psychiatric disorders impacted by the loss of FMRP.

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retardation protein and $GABA_A$ receptor beta 3 in adults with autism, Anatomical Record, in press, copyright (2011) with permission from John Wiley and Sons and 2) Fatemi, S.H., Kneeland, R.E., Liesch, S.B., Folsom, T.D., Fragile X mental retardation protein levels are decreased in major psychiatric disorders, Schizophrenia Research, 124(1–3):246–247, copyright (2010) with permission from Elsevier.

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