Neuropharmacology 60 (2011) 1221–1226

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

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

S. Hossein Fatemi [a,b,c,*], Timothy D. Folsom [a]

[a] Department of Psychiatry, Division of Neuroscience Research, University of Minnesota Medical School, 420 Delaware St SE, MMC 392, Minneapolis, MN 55455, USA
[b] Department of Pharmacology, University of Minnesota Medical School, 420 Delaware St SE, MMC 392, Minneapolis, MN 55455, USA
[c] Department of Neuroscience, University of Minnesota Medical School, 420 Delaware St SE, MMC 392, Minneapolis, MN 55455, USA

ARTICLE INFO

Article history:
Received 8 September 2010
Received in revised form
4 November 2010
Accepted 11 November 2010

Keywords:
Fragile X mental retardation protein
Brain
Autism
Schizophrenia
Dendrite
Metabotropic glutamate receptor

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.

This article is part of a Special Issue entitled 'Trends in Neuropharmacology: In Memory of Erminio Costa'.

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

* Corresponding author. Department of Psychiatry, Division of Neuroscience Research, University of Minnesota Medical School, MMC 392, 420 Delaware St SE Minneapolis, MN 55455, USA. Tel.: +1 612 626 3633; fax: +1 612 624 8935.
E-mail addresses: fatem002@umn.edu (S.H. Fatemi), folso013@umn.edu (T.D. Folsom).

0028-3908/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2010.11.011

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

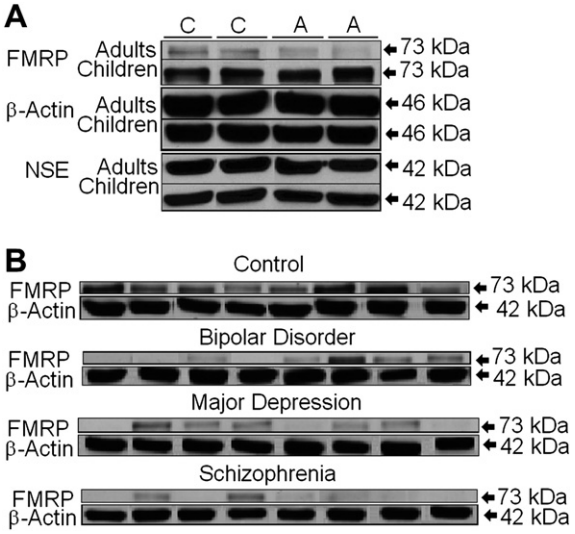

Fig. 1. Reduction of FMRP is subjects with autism (A), and subjects with bipolar disorder, major depression, and schizophrenia (B) vs. controls. **A:** Expression of FMRP, β-actin, and neuronal specific enolase (NSE) in cerebellar vermis from subjects with autism (A) and control subjects (C). **B:** 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.