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REVIEW

The Implication of AMPA Receptor in Synaptic Plasticity Impairment and Intellectual Disability in Fragile X Syndrome

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Summary

Fragile X syndrome (FXS) is the most frequently inherited form of intellectual disability and prevalent single-gene cause of autism. A priority of FXS research is to determine the molecular mechanisms underlying the cognitive and social functioning impairments in humans and the FXS mouse model. Glutamate ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPARs) mediate a majority of fast excitatory neurotransmission in the central nervous system and are critically important for nearly all aspects of brain function, including neuronal development, synaptic plasticity, and learning and memory. Both preclinical and clinical studies have indicated that expression, trafficking, and functions of AMPARs are altered and result in altered synapse development and plasticity, cognitive impairment, and poor mental health in FXS. In this review, we discuss the contribution of AMPARs to disorders of FXS by highlighting recent research advances with a specific focus on change in AMPARs expression, trafficking, and dependent synaptic plasticity. Since changes in synaptic strength underlie the basis of learning, development, and disease, we suggest that the current knowledge base of AMPARs has reached a unique point to permit a comprehensive re-evaluation of their roles in FXS.

Key words

Fragile X syndrome • Intellectual disability • AMPA receptors • Synaptic plasticity • Learning and memory

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Introduction

Fragile X syndrome (FXS) is one of the most common forms of intellectual disability and monogenic cause of autism spectrum disorders (ASD) (Harris *et al.* 2008, Rogers *et al.* 2001). In most cases, this disorder results from the transcriptional silencing of the fragile X mental retardation 1 (*fmr1*) gene on chromosome Xq 27.3, due to an excessive expansion of a CGG repeat found in the 5′-untranslated region (O'Donnell *et al.* 2002, Bagni *et al.* 2005, Santoro *et al.* 2012). The *fmr1* gene product, fragile X mental retardation protein (FMRP), a selective RNA-binding protein is absent in FXS (Antar *et al.* 2006, Bassell *et al.* 2008, Till *et al.* 2012). FMRP modulates expression of nearly a third of

pre- and post-synaptic proteomes (Liao *et al*. 2008, Darnell *et al*. 2011, Klemmer *et al*. 2011) and functions at both pre- and post-synaptic compartments (Till *et al*. 2010, Deng *et al*. 2013, Patel *et al*. 2013). In its absence, the transcripts are over translated in the dendrites and axons, which are typically regulated by FMRP (Bassell *et al*. 2008, Waung *et al*. 2009, Dierssen *et al.* 2006). In particular, one of the primary defects associated with the absence of FMRP appears to be excessive synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPARs) internalization in response to the signaling of metabotropic glutamate receptors (mGluR) (O'Donnell *et al*. 2002, Nakamoto *et al*. 2007, Bear *et al*. 2004, Huber *et al*. 2002). Therefore, FXS is partially a result of exaggerated internalization of synaptic AMPARs.

Since AMPARs are important for neuronal development, synaptic plasticity, and cognitive function (e.g. learning and memory) (Hamad *et al*. 2011, Urbanska *et al*. 2008, Malenka *et al*. 2003), the effects of FMRP on complex pathways that control AMPARs insertion and removal from the synaptic membrane could have a large effect on synaptic strength and excitability. In this review, we discuss the specific contribution of AMPARs to FXS disorders by their effect on multiple levels and highlight how defects in AMPAR expression and trafficking are important to fragile X intellectual disability. We suggest that the knowledge base of AMPARs has reached a unique point to permit a comprehensive re-evaluation of their role in FXS.

We performed a desk review of journal publications on FXS and AMPAR, and implemented a comprehensive search strategy for different categories using a combination of text words and indexing terms (MeSH) in PubMed, China National Knowledge Infrastructure, Wanfang databases over the last three decades (1986 – 2016). To obtain the information relevant to fragile mental retardation protein or *fmr1* and AMPAR and glutamate, we used the keywords “fragile X syndrome” or “fragile mental retardation protein” or “*fmr1*” or “neurodevelopmental disorders” and “AMPAR” or “Glutamate” or “mGluR1” or “mGluR5.” We included only those publications written in English language and excluded book reviews, editorials, errata, conference proceeding overviews, and abstracts.

Genetic basis and cognitive disability in FXS

Fragile X syndrome was discovered in association with the fragile site of the X chromosome in two brothers in 1969 by Lubs and colleagues (Lubs *et al*. 1969). In 1991, the gene responsible for FXS, *fmr1*, was identified and scientists developed a specific associated DNA test (Verkerk *et al*. 2008, Oberle *et al*. 1991, Davids *et al*. 1990). The normal allele of the *fmr1* gene typically has 5 to 40 CGG repeats in the 5' untranslated region. The abnormal alleles of dynamic mutations (Fig. 1) include the full mutation (>200 CGG repeats), premutation (55-200 CGG repeats), and the gray zone mutation (45-54 CGG repeats) (Sutcliffe *et al.* 1992). Full mutation alleles are associated with intellectual disability and behavioral impairments (e.g. impaired social interaction and communication) (Verkerk *et al*. 2008, Oberle *et al*. 1991, Fu *et al*. 1991). Carriers of premutation alleles are at risk for adult-onset neurodegenerative disorder known as fragile X-associated tremor/ataxia syndrome (Hagerman *et al*. 2013), and female carriers are at risk for fragile X-associated primary ovarian insufficiency. The latter condition is associated with fertility problems and an earlier than normal menopause (Sullivan *et al*. 2011, Sherman *et al*. 2014).

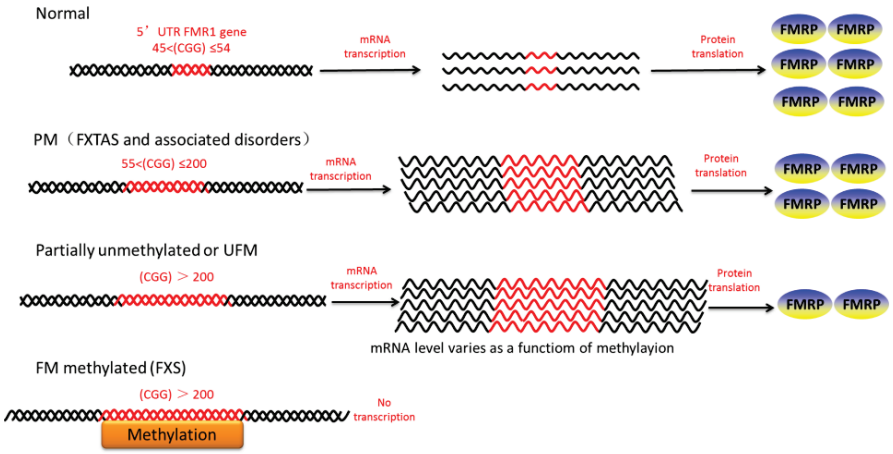

Fig. 1. The abnormal alleles of dynamic mutations include the full mutation (>200 CGG repeats), premutation (55-200 CGG repeats) and the gray zone mutation (45-54 CGG repeats).

Patients with FXS typically have a significant learning disability with an intellectual quotient (IQ) that declines from about 80 at 5 years of age to about 50 through the pubertal years (Skinner *et al*. 2005, Loesch *et al*. 2004). Cognitive difficulties include impaired working and short-term memory, executive function, arithmetic, and visuospatial abilities (Kemper *et al*. 1988). Mental health symptoms in patients with FXS include anxiety, depression, hyperactivity, impulsivity, and aggression (Tsiouris *et al*. 2004). Because the disorder is X-linked, women are generally less affected than men, particularly with regard to cognitive abilities. However, women tend to have greater risk for mental health problems relative to the general population (De Vries *et al*. 1996, Freund *et al*. 1993).

AMPARs expression in developmental phases of FXS

Functional AMPARs are expressed throughout the brain in various tetrameric assemblies of GluA1, GluA2, GluA3, and GluA4 (Beneyto *et al*. 2004) (Fig. 2), and play a prominent role in neuronal development. During the neonatal developmental period, some synapses are named as silent synapses due to the lack of AMPARs at their resting state and instead only contain NMDARs (Nicoll *et al*. 1997, Liao *et al*. 1995). From a functional standpoint, synapses of this nature are rendered "silent" to glutamate release since NMDARs are tonically blocked by Mg^{2+} at resting membrane potentials. The proportion of AMPAR-deficient synapses is greater in the neonatal central nervous system (CNS) than in the adult (Wu *et al*. 1997, Petralia *et al*. 1999, Xiao *et al*. 2004), and the subunit composition and relative abundance of AMPA and NMDA receptors are adjusted as crucial steps in the establishment of a functionally mature synapse (Bellone *et al*. 2007). However, the loss of FMRP leads to a substantial decrease in the AMPA/NMDA ratio between postnatal days 4 (P4) and P7, with the lowest AMPA/NMDA ratio occurring just before closure of the normal critical period (Harlow *et al*. 2010). Therefore, the number of silent synapses is increased in the critical period in *fmr1* KO neurons. In WT mice, most of these silent synapses are unsilenced due to the increased AMPAR subunits expression in the cell membrane during the later developmental period, but one study found increased silent synapses that persisted later in development with a temporal delay in the window for synaptic plasticity in *fmr1* KO mice (Harlow *et al*. 2010). In another *fmr1* KO2 mouse model, there was also a significantly lower AMPA/NMDA ratio compared with WT mice at P14, but not at 6 or 7 weeks (Pilpel *et al*. 2009). This new *fmr1* KO2 line is a more versatile *fmr1 in vivo* KO model by flanking the promoter and first exon of *fmr1* with lox P sites. The new line expresses no FMRP and lacks detectable *fmr1* transcripts (Mientjes *et al*. 2006, Oostra *et al*. 1994). Therefore, the lower AMPA/ NMDA ratio in *fmr1* KO2 mice is the direct result of the absence of FMRP and *fmr1* transcripts. This difference in the AMPA/NMDA ratio at P14 is probably related to an up-regulation of the NMDA receptor component concurrent with a down-regulation of the AMPAR component (Pilpel *et al*. 2009). In line with up-regulation of the NMDA component, the induction of NMDA receptor-dependent LTP following a low-frequency pairing protocol is increased in *fmr1* KO2 mice only at this developmental stage (Pilpel *et al*. 2009). Taken together, the expression of AMPARs in various brain regions is decreased during postnatal development in *fmr1* KO mice (Neves *et al*. 2008, Davidkova *et al*. 2007, Jin *et al*. 2004).

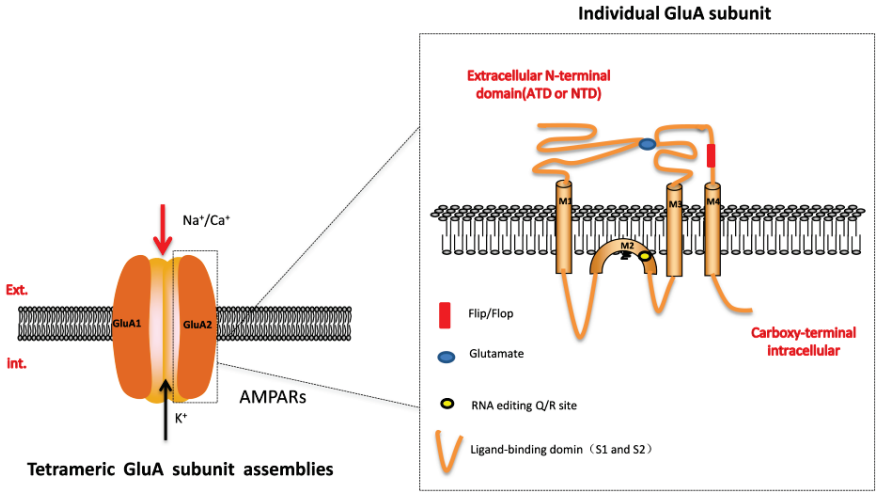

Fig. 2. AMPA receptors (AMPARs) are heteromeric assemblies of four core subunits, GluA1, GluA2, GluA3, and GluA4. They mediate most fast excitatory neurotransmission. The different combinations are not completely variable. In CA1 neurons, for instance, mostly express GluA1/GluA2 and GluA2/GluA3 are heteromers, while a smaller proportion of GluA1/GluA1 are homomers. GluA2/GluA2 and GluA3/GluA3 can't be formed.

The alteration of AMPARs expression in FXS animal model

There are multiple important processes involved in AMPARs expression and their synaptic function including protein synthesis, proteasomal degradation, alternative splicing, and mRNA trafficking. A component in the regulation of AMPAR subunits and associated protein complex synthesis is FMRP, which is localized to dendritic spines (Feng *et al*. 1997) and traffics within dendrites and at the synapses after stimulation (Antar *et al*. 2004, Muddashetty *et al*. 2007) (Fig. 3).

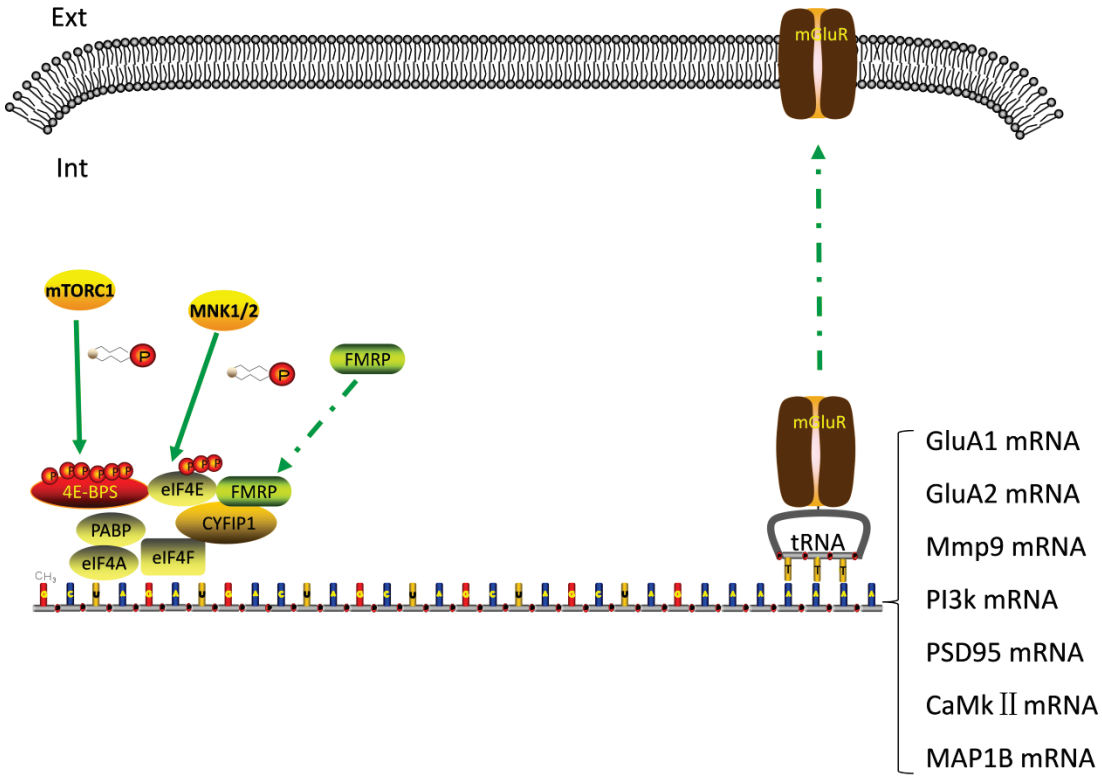

Fig. 3. The possible targets of FMRP in dendritic spines. FMRP is a RNA binding protein that transports, stabilizes, and regulates the translation of hundreds of mRNAs at the synapse. It has been suggested that it plays a role in regulation of the local synthesis of AMPAR subunits and associated protein complexes, including MMP 9, PI3K, PSD95, CaMKII and MAP1B. The symbols used in the Figure 3 are listed below: Ext=extracellular space; Int=intracellular space; mTOR = mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1; Mnk1/2=MAPK-interacting kinase 1 and 2 (Mnk1/2); eIF4=eukaryotic translation initiation factor 4E; EIF4EBP1Eukaryotic translation initiation factor 4E-binding protein 1; PABP=Poly (A)-binding protein; CYFIP1=Cytoplasmic FMR1-interacting protein 1; mGluRs=metabotropic glutamate receptors; PI3Ks=phosphatidylinositol-3-kinases; MMP-9=Matrix metallopeptidase 9; PSD-95=postsynaptic density protein 95; CaMKII=Ca^{2+}/calmodulin-dependent protein kinase II; MAP1B=Microtubule-associated protein 1B.

Multiple preclinical and primary neuron studies have suggested that the local synthesis AMPAR subunits are dysregulated in *fmr1* KO mice (Bear *et al*. 2004, Huber *et al*. 2002, Muddashetty *et al*. 2007, Soden *et al*. 2010, Garber *et al*. 2008). Indeed, in *fmr1* KO mice, GluA1 is decreased in the cortical synapses (Li *et al*. 2002), hippocampal neurons (Grossman *et al*. 2010), and synapse membrane (Nakamoto *et al*. 2007, Guo *et al*. 2015, Hu *et al*. 2008). The FXS mGluR theory posits that FMRP loss within the mGluR signaling pathway leads to several downstream consequences of mGluR activation and increased internalization of AMPAR subunits (Nakamoto *et al*. 2007, Huber *et al*. 2007, Chuang *et al*. 2005). The role of FMRP in excessive mGluR-dependent internalization of AMPARs has been demonstrated in normal rat neuronal hippocampal cultures using FMRP siRNA (Nakamoto *et al*. 2007). Similarly, the internalization of surface GluA1 is impaired in *fmr1* KO prefrontal cortex (PFC) and amygdala neurons (Wang *et al*. 2010, Suvrathan *et al*. 2010). The changes in AMPAR subunit expression are also involved in alterations in AMPAR mRNAs trafficking. Interestingly, while their mRNA levels remain unchanged in *fmr1* KO mice, their subcellular localization is altered. The quantitative analysis of mRNA levels in FMRP-specific immunoprecipitations from synaptoneurosomes has

substantiated the association of FMRP with GluA1 and GluA2 mRNAs (Muddashetty *et al*. 2007). In addition, studies have also linked Strial-Enriched protein Tyrosine Phosphatase (STEP) dysregulation in *fmr1* KOs to aberrant endocytosis of AMPARs (Huber *et al*. 2002, Zhang *et al*. 2008) (Fig. 4).

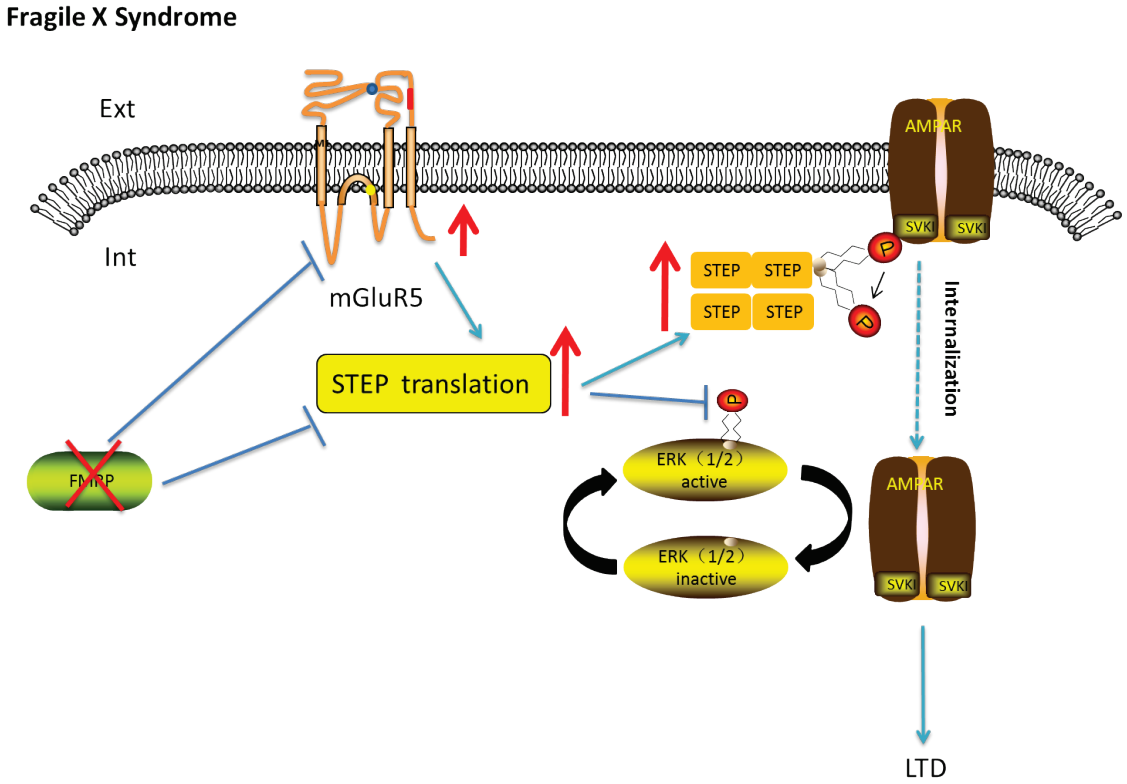

Fig. 4. The mGluR theory refer to the pathophysiology in FXS, which proposes that loss of FMRP within mGluR signaling pathway leads to excessive expression of several downstream consequences of mGluR activation, such as STEP, and increased internalization of AMPAR subunits.

Our prior work indicated that 7, 8-dihydroxyflavone (7, 8-DHF), an identified high affinity tyrosine receptor kinase B (TrkB) agonist, enhances expression of GluA1 at the synapses in *fmr1* KO mice (Tian *et al*. 2015). Potentially related to drug-induced increases in AMPAR subunits at synapses, 7, 8-DHF leads to phosphorylation of specific serine sites on subunits Ser818 and Ser813 of GluA1, and Ser880 of GluA2, as well as phosphorylation of TrkB, calcium/calmodulin-dependent protein kinase II (CaMKII), and protein kinase C (PKC) (Tian *et al*. 2015). Collectively, FMRP ablation results in glutamatergic signaling maturation dysregulation (Bear *et al*. 2004). Such AMPAR signaling dysregulation at the synapses may impair molecular composition control of the postsynaptic density and consequently alter synaptic transmission. This alteration in synaptic transmission could lead to impairment of neuronal plasticity and produce neurogenesis-associated learning deficits that have been observed in *fmr1* KO mice and patients with FXS (Muddashetty *et al*. 2007, Wang *et al*. 2011, Guo *et al*. 2011). Some chemicals (e.g. 7, 8-DHF) induce synapse expression of AMPA GluA1 through increasing phosphorylation of AMPAR subunits, which then remedies cognitive dysfunction and spine abnormalities in *fmr1* KO mice (Tian *et al*. 2015).

FMRP has two conserved autosomal paralogs, FXR1P and FXR2P (also known as FXR1 and FXR2), and all three RNA-binding proteins are enriched in neurons (Li *et al*. 2014, Darnell *et al*. 2009). Studies have shown that FMRP and its paralogs have the ability to interact with one another, and that FMRP and FXR2P double KO mice show greater neurobehavioral abnormalities (e.g. hyperactivity, exaggerated locomotor activity, contextual fear conditioning) compared to single-mutant mice (Spencer *et al*. 2014, Spencer *et al*. 2011). FXR2P reduces Noggin mRNA stability in adult neural stem cells (Guo *et al*. 2011) and binds to GluA1 mRNA to enhance stability and protein production (Guo *et al*. 2011). These results suggest a role for FMRP in the

regulation of the local synthesis of AMPAR subunits and associated protein complexes.

The alteration of AMPARs trafficking in FXS

AMPAR trafficking is a driving process for synaptic plasticity that underlies learning and memory, and involves the dynamic processes of exocytosis, endocytosis, endosomal recycling (Pilpel *et al*. 2009, Wang *et al*. 2010, Hanley *et al*. 2014, Haering *et al*. 2014, Chater *et al*. 2014, Kessels *et al*. 2009, Perestenko *et al*. 2003). It is well known that FMRP has significant roles in regulating the synaptic delivery of GluA1 and AMPAR trafficking (Nakamoto *et al*. 2007, Hu *et al*. 2008) (Fig. 4). Aberrant AMPAR trafficking and consequent synaptic defects are strongly implicated in FXS (Nakamoto *et al*. 2007, Yan *et al*. 2005, McBride *et al*. 2005). Also, some of the defects are associated with the lack of FMRP as demonstrated in FMRP-absent Drosophila and mouse models (Yan *et al*. 2005, McBride *et al*. 2005). One alteration in AMPAR trafficking is involved in the regulation of small GTPase, Ras, and Rap signaling (Isaac *et al*. 2007, Gu *et al*. 2007), and many synaptic proteins in the NMDA receptor (NMDAR)-Ras-PI3K/PKB signaling interactome (Darnell *et al*. 2013, Ascano *et al*. 2012, Kielland *et al*. 2009). FMRP modulates the synaptic trafficking of GluA1 through Ras (Soden *et al*. 2009, Lim *et al*. 2009). LTP is reduced by approximately 50 % in *fmr1* KO mice due to selective impairment of synaptic trafficking of GluA1 and GluA4-containing AMPARs, which results from deficient Ras activity (Hu *et al*. 2008). Enhancing Ras signaling restores GluA1-containing AMPARs synaptic delivery and LTP in *fmr1* KO mice (Hu *et al*. 2008). Hence, FMRP deficiency leads to reduced membrane and synaptic delivery of AMPAR subunits and reduced AMPA current levels (Hu *et al*. 2008).

Many molecules interact with AMPARs and are involved in their trafficking (Joyce *et al*. 2010, Wang *et al*. 2012). Some of those molecules implicated in FXS include tumor necrosis factor alpha (TNFα) (Stellwagen *et al*. 2006), retinoic acid (Soden *et al*. 2010), PICK1 (Anggono *et al*. 2011), activity-regulated cytoskeletal gene and protein (Arc/Arg3.1) (Shepherd *et al*. 2006), and phosphatidylinositide-3 kinase (PI3K) signaling (Hou *et al*. 2008). In addition, proteins regulating AMPAR endocytosis such as Arc, microtubule associated protein 1B (MAP1B), STEP, amyloid precursor protein (APP) (Fig. 5), and termed LTD proteins, are upregulated in neuronal dendrites in *fmr1* KO mice and stable during mGluR-LTD.

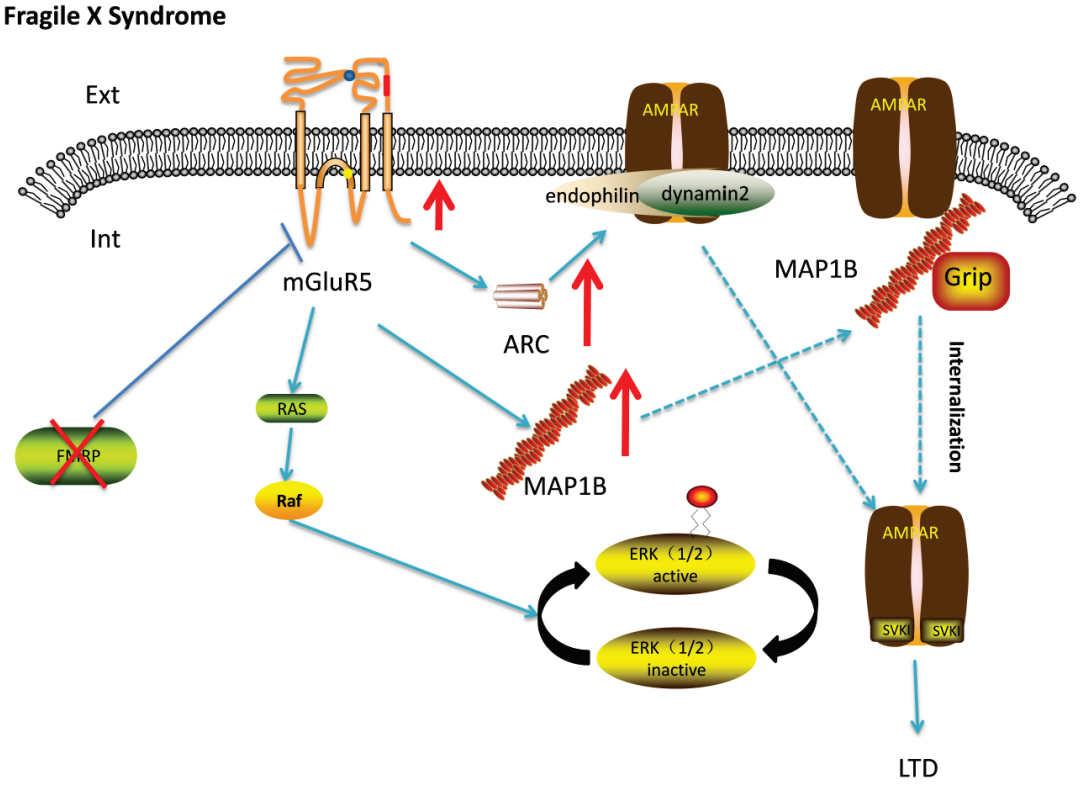

Fig. 5. The molecules termed LTD proteins that are implicated in FXS, such as Arc, MAP1B, and GRIP are basally upregulated in neuronal dendrites from *fmr1* KO mice, and induce the internalization of AMPAR subunits.

The alteration of AMPARs synaptic transmission and plasticity in FXS

AMPARs mediate synaptic plasticity expression related to cognitive processes such as LTP, LTD, and homeostatic plasticity. Defective AMPAR-mediated synaptic transmission and plasticity have emerged as a common phenotype in FXS animal models (Muddashetty *et al*. 2007, Li *et al*. 2002, Darnell *et al*. 2013, Meredith *et al*. 2007, Lauterborn *et al*. 2007, Larson *et al*. 2005, Koekkoek *et al*. 2005). Many studies have identified synaptic plasticity deficits that involve LTP in the hippocampus (Li *et al*. 2002, Darnell *et al*. 2013, Lauterborn *et al*. 2007, Larson *et al*. 2005, Wilson *et al*. 2007, Desai *et al*. 2006, Zhao *et al*. 2005) and other cortical regions such as the thalamic afferents to the lateral amygdala (LA) (Wang *et al*. 2010), and the PFC in *fmr1* KO mice (Xu *et al*. 2005, Wang *et al*. 2008). FMRP deficiency in adult neural stem cells leads to reduced neuronal production and maturation, and reduced LTP in the cortex (Li *et al*. 2002). The enhanced internalization of AMPARs or impaired synaptic delivery of GluA1 results in a selective loss of GluA1 dependent LTP (Darnell *et al*. 2013, Lauterborn *et al*. 2007, Xu *et al*. 2012, Wang *et al.* 2008, Hou *et al*. 2006). The second form of hippocampal altered synaptic plasticity in *fmr1* KO mice is hippocampal gp I mGluR LTD, which is triggered by the activation of gp I mGluR (Bear *et al*. 2004, Huber *et al*. 2002). Indeed, dendritic protein synthesis induced by mGluR-dependent LTD, such as MAP1b, CaMKIIα, Arc, and STEP, is elevated in slice cultures from *fmr1* KO mice and fails to show induction (Darnell *et al*. 2011, Waung *et al*. 2009, Hou *et al*. 2006) (Figs 4 and 5). Correspondingly, in the *fmr1* KO mouse, synaptic plasticity (mGluR-dependent LTD) in the cerebellum is altered (enhanced) and results in learning deficits) (Huber *et al*. 2006). The third form of hippocampal altered synaptic plasticity in *fmr1* KO mice is homeostatic plasticity dependent on retinoic acid (RA) (Soden *et al*. 2010). Synaptic activity increases synaptic plasticity potential by inducing RA synthesis, which activates postsynaptic synthesis of AMPARs in dendrites and promotes synaptic insertion of newly synthesized AMPARs. FMRP is essential for this process, and RA-dependent dendritic translation of GluA1 is impaired in *fmr1* KO mice (Irwin *et al*. 2000, Braun *et al*. 2000, Comery *et al*. 1997).

A study performed in primary hippocampal neuron cultures from *fmr1* KO mice demonstrated a delay in synapse maturation, but found no differences in miniature AMPAR-mediated currents (Braun *et al*. 2000). Another study in organotypic hippocampal slice cultures reported small, but detectable reductions in AMPA miniature currents in *fmr1* KO cells. The reductions were only detectable when pairs of cells, *fmr1* KO and WT controls were patched within the same culture slice (Pfeiffer *et al*. 2007). Taken together, these studies demonstrated that the current in AMPAR mEPSCs is changed in *fmr1* KO mice and that there is impairment in GluA1/2 signals. The impaired GluA1/2 signals in *fmr1* KO mice highlights the possibility that restoration of normal GluA1-dependent synaptic plasticity may reverse prominent learning deficits associated with FXS. This possibility is further supported by the findings that 7, 8-DHF induces synapse expression of AMPA GluA1 and ameliorates cognitive and spine abnormalities in *fmr1* KO mice (Tian *et al*. 2015).

Given the proposed hypofunction associated with AMPARs, it has been suggested that the synthetic compounds Ampakines, which are positive allosteric modulators, may be beneficial for clinical therapeutics. Ampakines allow glutamate to have a prolonged effect on AMPARs and strengthen memory retention on multiple tasks in many different species (Lynch *et al*. 2006). To date, the Ampakine CX-516 has progressed into Phase II clinical trials to assess its value in treating FXS (Berry-Kravis *et al*. 2006, Danysz *et al*. 2002). Although the study reported no adverse side-effects associated with CX-516, the Ampakine compound relative to placebo provided little improvement in behavioral tests (Berry-Kravis *et al*. 2006).

Conclusions

Over the past two decades, efforts have been made to elucidate the molecular and cellular events that underlie synaptic dysfunction in FXS. Findings from multiple studies have implicated AMPARs dysfunction in FXS. AMPAR alterations in FXS animal models are usually manifested as changes in the expression and trafficking of receptors. Other parallel mechanisms associated with FXS include AMPAR phosphorylation/dephosphorylation, alterations in the trafficking of AMPAR mRNAs, and synthesis/degradation of the receptor proteins. These hypothesized mechanisms of FXS are supported through human genetic studies, clinical trials, postmortem brain studies, animal models, and *in vitro* cell cultures.

Findings from such studies substantiate the need to monitor and manipulate synaptic AMPAR trafficking and restore AMPAR levels in order to improve cognitive function and normalize other impairments in FXS preclinical models. This new avenue of study could lead to improved understanding of the mechanisms underlying FXS and development of new clinical therapeutic applications.

Conflict of Interest

Dr. McClintock reports honoraria as teaching faculty from TMS Health Solutions. The other authors declare no conflict of interest.

Acknowledgements

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