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Fragile X syndrome: Mechanistic insights and therapeutic avenues regarding the role of potassium channels

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Abstract

Fragile X syndrome (FXS) is a common form of mental disability and one of the known causes of autism. The mutation responsible for FXS is a large expansion of the trinucleotide CGG repeats which leads to DNA methylation of the fragile X mental retardation gene 1 *(FMR1)* and transcriptional silencing, resulting in the absence of fragile X mental retardation protein (FMRP), an mRNA binding protein. Although it is widely known that FMRP is critical for metabotropic glutamate receptor (mGluR)-dependent long-term depression (LTD), which has provided a general theme for developing pharmacological drugs for FXS, specific downstream targets of FMRP may also be of therapeutic value. Since alterations in potassium channel expression level or activity could underlie neuronal network defects in FXS, here we describe recent findings on how these channels might be altered in mouse models of FXS and the possible therapeutic avenues for treating FXS.

Keywords

fragile X syndrome; FMRP; mGluR theory; potassium channels

Introduction

Fragile X syndrome (FXS), with an incidence of 1 in 5,000 males [1], causes mild to severe mental disability, often accompanied by autism-like behaviors, developmental delay, increased susceptibility to seizures, and macroorchidism in males [2]. A key advance for understanding FXS was the cloning of the fragile X mental retardation gene 1 *(FMR1)* [3*] located at Xq27.3, the diagnostic fragile site on the X chromosome [4], and the generation of the *fmr1* knockout (KO) mouse line [5*]. In affected individuals, expansion of a CGG repeat (>200) located in the 5' untranslated region (UTR) of *FMR1* [6] leads to hypermethylation of both the CGG repeats and the *FMR1* promoter, transcriptional silencing, and loss of its protein product fragile X mental retardation protein (FMRP) [7, 8]. In addition, a small number of deletions and missense mutations in the *FMR1* gene have been linked to FXS [9-11]. Multiple symptoms seen in FXS patients, including the altered spine morphology [12-14], are recapitulated in *fmr1* KO mice [15, 16], which also display compromised learning, abnormal behavior and altered synaptic plasticity [17]. The *fmr1* KO mouse is therefore a useful system for mechanistic studies of FXS.

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FMRP is ubiquitously expressed in mammalian tissues [18], and its abundance in the brain and testes is consistent with FXS symptoms [18, 19]. FMRP is expressed primarily in neurons in the brain [18] and can bind target mRNAs directly or indirectly [20]. FMRP has multiple RNA-binding motifs including two K homology domains (KH1 and KH2) and the arginine-glycine-glycine (RGG) box [21**], whose affinity for certain mRNAs may be regulated by the methylation status of the arginines in the RGG box [22]. In addition to these conserved domains, other regions of FMRP have also been implicated in protein-protein interactions that are important for its function [21**].

Multiple U-rich pentamers reside in both the coding region and 3'UTR of some FMRP target mRNAs [23], and a U-rich region in the 5'UTR of hASH1 also binds FMRP [24]. The C-terminal RGG box recognizes the G quadruplex [25**, 26] likely present in targets such as the FMRP, MAP1b, and Sema3F mRNAs [21**]. Another secondary structure known as the kissing complex binds the KH2 domain *in vitro* [27]. Moreover, FMRP also binds to the superoxide dismutase 1 (Sod1) mRNA through a novel RNA structure termed Sod1 stem loops interacting with FMRP (SoSLIP) [28], which interacts with the RGG box-containing C-terminal domain and competes with G quadruplex for FMRP binding [28].

The dense and immature dendritic spines associated with FXS [12-14] indicate that FMRP regulates dendritic development and function. Because FMRP is localized to dendrites and spines, it could regulate local protein synthesis to modulate spine development and synaptic plasticity [20]. Indeed, many of the FMRP target mRNAs localize to dendrites [21**], and FMRP may regulate mRNA localization [29], stability [30], or translation [31, 32] in central neurons [33, 34].

FMRP inhibits translation of most of its target mRNAs, which has been demonstrated in rabbit reticulocyte lysate [35], in *Xenopus laevis* oocytes [36] and in immortalized cells from an *fmr1* KO mouse [37]. In addition, brains and synaptosomes from *fmr1* KO mice have an overabundance of FMRP targets such as Map1b, Arc, and CamKIIα [38, 32], and they have the CamKIIα, PSD-95, and GluR1/2 mRNAs shifted to actively translating polyribosomes [31]. Surprisingly, FMRP seems to upregulate the translation of Sod1 mRNA by strengthening SoSLIP's ability to activate translation [28]. Thus far, only a small number of mRNAs have been verified as FMRP targets [21**], while the molecular mechanisms for FMRP regulation of translation remain to be elucidated.

FMRP repression of its targets may be relieved to mediate dynamic regulation – a process that may involve phosphorylation regulation of FMRP [39-41], which contains a highly conserved serine (human Ser500, murine Ser499, *Drosophila* Ser406) that is phosphorylated [39] to enable FMRP repression of translation [39, 42*, 43**]. Phosphorylated FMRP is associated with stalled ribosomes, whereas unphosphorylated FMRP allows ribosomes to proceed with translation [39], and may also associate with Dicer [44].

Targeted treatments for neurodevelopmental disorders such as FXS have become a feasible therapeutic strategy following the development of appropriate animal models [45**, 46**], such as the *fmr1* KO mice. Recent studies of FXS have opened new avenues of investigation leading to the rational design of potential therapeutics for FXS. Besides FMRP, the metabotropic glutamate receptor 5 (mGluR5) signaling pathway may provide a target for the treatment of FXS. Recent studies have also implicated abnormal potassium channel activity in FXS, which will be discussed later in this review. Hence, mGluR5 and potassium channels have emerged as targets for developing novel therapeutic reagents for FXS.

Current strategy for targeted treatment based on the mGluR theory

Because group I mGluR-dependent long-term depression (mGluR-LTD) is a major form of synaptic plasticity involving synaptic regulation of local protein synthesis of dendritically localized mRNAs, mGluR-LTD and the antagonistic regulation by FMRP have been studied extensively. Given that mGluR-LTD is enhanced in the hippocampus of *fmr1* KO mice [47**, 48], Huber et al. [47**] proposed that FMRP limits LTD by inhibiting mGluR-dependent translation of dendritic mRNAs encoding the hypothetical "LTD protein(s)", so that FMRP synthesis induced by mGluR5 would provide a brake to prevent runaway synaptic protein synthesis. The increase in cerebral protein synthesis in *fmr1* KO mice [49, 50*] may lead to the internalization of α-amino-3-hydroxyl-4-isoxazole propionic acid receptors (AMPAR), a key step in mGluR-LTD [51**, 52**]. In addition, dephosphorylation of FMRP following mGluR activation correlates with the release of translational inhibition of FMRP target mRNAs [40, 42*], with protein phosphatase 2A (PP2A) and ribosomal protein S6 kinase 1 (S6K1) as the primary phosphatase and kinase [40, 41]. Both the persistently enhanced mGluR-LTD and the inability of synaptic inputs to further increase protein synthesis uncovered in these studies are likely culprits in FXS, possibly involving FMRP targets such as MAP1b, eEF1A, Arc, CaMKIIα, PSD-95, SAPAP3, and APP [33, 53, 21**].

The hypothesis that overactive mGluR5 functions mediate many of the symptoms of fragile X suggests that mGluR5 antagonism may be a plausible therapeutic strategy for the disease. 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a potent negative allosteric modulator of mGluR5 [54] that crosses the blood-brain barrier, can rescue behavioral and cognitive deficits in mouse models of FXS [55*, 56*]. Acute administration of MPEP reduces audiogenic seizures and the abnormal response of *fmr1* KO mice in an open field test of anxiety-like phenotypes [55*]. MPEP also rescues other deficits including AMPAR internalization defects [57], prolonged epileptiform discharges in hippocampal slices [58], deficits in prepulse inhibition of startle [56*], decreased mRNA granule expression [59], excess protein synthesis in hippocampal slices [60], increased density of dendritic filopodia in hippocampal cultures [56*], and hyperactivity of glycogen synthase kinase-3 [61]. These studies have prompted development of novel therapeutic interventions; several clinical trials of drugs that target the mGluR pathway are currently underway [45**, 46**].

As a crucial validation of the mGluR theory, genetic reduction of mGluR5 in *fmr1* KO mice rescues many of the disease-related phenotypes [50*, 62], but not macroorchidism [50*], and provides compelling evidence that manipulating mGluR5 signaling can reverse fragile X–related phenotypes across species. This indicates that mGluR5 is a viable target for the treatment of FXS.

MPEP can rescue several major defects of *fmr1* KO mice, but not the deficit in long-term potentiation (LTP), a cellular correlate for learning and memory. While *fmr1* KO mice display LTP deficits in various brain regions including the hippocampus [63*, 64*, 65], in the few brain areas surveyed thus far MPEP fails to correct the deficit in LTP [66, 67]. This indicates that not all synaptic defects may be amenable to group I mGluR-targeted intervention [46**]. Moreover, some of the proposed FMRP target proteins such as PSD95 do not show the expected basal upregulation in *fmr1* KO mice [30]. Given that there are limitations of the current attempts in FXS treatment, it is important to extend our understanding of FMRP functions beyond those that involve mGluR signaling, and to explore other therapeutic avenues.

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The search for additional strategies for targeted treatment

Identification of potassium channels as FMRP targets

FMRP binds ~4% of the mRNA in the mammalian brain [68*]. Over 400 putative mRNAs are found to associate with FMRP using various methods [69**, 70, 71], although fewer than 20 of these have been validated biochemically [21**]. A recent study used high-throughput sequencing of RNAs isolated through cross-linking immunoprecipitation (HITS-CLIP) has identified FMRP target mRNAs in neurons [72**], providing evidence supporting the notion that FMRP causes ribosomes to stall during the elongation phase of translation [72**]. Another approach towards an understanding of FMRP function has been the search for proteins that interact directly with FMRP or that are components of the FMRP-containing mRNP complex. Several proteins such as FXR1P, FXR2P, 82-FIP, NUFIP1, CYFIP1 and CYFIP2 have been characterized as FMRP interacting proteins to date [73]. Strikingly, these various approaches also identified several potassium channel mRNAs as well as a potassium channel protein as FMRP targets, as detailed below.

There are many different potassium channels in the nervous system including inward rectifier and leak potassium channels that control the resting membrane potential [74, 75], and voltage-gated potassium channels that regulate the action potential waveform [76]. Potassium channels have to be at the right place in the right number to endow individual neurons with their specific character. Their biophysical properties together with their spatial distribution define the signaling characteristics of a neuron.

Mouse models of FXS show defects in three kinds of potassium channels, the Na^+-activated K^+ channel (K_{Na}) Slack-B [77**], and the voltage-gated K^+ channels Kv3.1b [78**] and Kv4.2 [43**]. FMRP binds the mRNAs for Kv3.1b and Kv4.2, and also interacts directly with the Slack-B protein to modulate its activity in heterologous expression systems [77**, 78**, 43**] (Figure 1). We will discuss how these channels might be altered in *fmr1* KO mice.

The Slack Potassium Channel as a Therapeutic Target for FXS in the Auditory System

Individuals with FXS have a range of perceptual deficits in processing auditory stimuli, and may be particularly sensitive to loud sounds [79]; they also have fluctuations in their speech pattern [80]. These symptoms interfere with brain functions such as attention, learning, language development, and social interactions. The integrity of neuronal encoding and processing of sensory inputs depends on ion channels that regulate the action potential waveform and firing pattern, such as Slack-B that has a large cytoplasmic C-terminal domain [81] and is widely expressed in the brain [81].

A recent study has found that FMRP directly binds to the C-terminus of the Slack-B channel protein and causes a several-fold activation of Slack-B channel activity by increasing channel openings (77**), thus providing the first example for direct binding of FMRP to a membrane protein (Figure 1a). Moreover, Slack potassium currents in the medial nucleus of the trapezoid body (MNTB) of the auditory brainstem are reduced by about 50% in *fmr1* KO mice (Figure 1a). Slack is required for accurate timing of action potentials of these central auditory neurons in response to synaptic stimuli [82]. Defects with this potassium channel function may contribute to the difficulty of some FXS patients to adapt to the ambient auditory environment [83]. Slack activators may thus be considered as novel therapeutic agents that could act either independently or in concert with agents that affect group I mGluRs, which may in turn regulate Slack channels [84].

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Alteration in Kv3.1 Levels in Auditory Brainstem Nuclei of fmr1 KO Mice

Studies have shown that *fmr1* KO mice exhibit abnormal sensitivity to auditory stimuli including hyper reactivity and the induction of audiogenic seizures [50*, 55*]. While audiogenic seizures have not been reported in Fragile X patients, the onset and manifestation of autistic behavior in these individuals correlates with auditory hypersensitivity [2, 17]. Audiogenic seizures are thought to arise from increased excitation in auditory nuclei rather than an overall increase in brain excitability. Kv3.1 channels are at particularly high levels in neurons of auditory nuclei [85] and their fast gating kinetics permits neurons to fire prolonged trains of action potentials at very high frequencies with little adaptation [86].

Kv3.1 mRNA has been identified [25**] and validated [78**] as a binding target for FMRP. The physiological role of Kv3.1 channels is to allow specific types of neurons to fire at very high rates [83], which helps in decoding loud and diverse sounds. Moreover, the faithful delivery of all sound frequencies is dependent on a precise tonotopic gradient of Kv3.1b splice isoform expression within MNTB of the auditory brainstem; Kv3.1b levels are highest at the medial end, which corresponds to high auditory frequencies [83]. Disruption of this auditory space code, or map, due to the Kv3.1b mysregulation would be expected to interfere with auditory processing in auditory nuclei of the brain stem and in the auditory cortex.

To explore the regulation of the Kv3.1b by FMRP, Strumbos et al. [78**] investigated Kv3.1b immunoreactivity and potassium currents in the auditory brainstem sound localization circuit of male mice by exposing animals to high-frequency, amplitude-modulated sound stimuli, which elicit predictable and stereotyped patterns of input to the anterior ventral cochlear nucleus (AVCN) and MNTB. While wild-type (WT) animals show a tonotopic gradient with Kv3.1b expression in the MNTB, *fmr1* KO mice display dramatically flattened gradients in tonotopicity as shown by the Kv3.1b immunoreactivity and K^+ currents at the basal condition (Figure 1b). Moreover, after 30 min of acoustic stimulation, the levels of Kv3.1b immunoreactivity were significantly elevated in both the MNTB and AVCN of WT, but not *fmr1* KO mice. This finding suggests that auditory neurons are likely to be hyperexcitable in FXS individuals and also suggests that FMRP is necessary for maintaining the gradient of Kv3.1b protein levels across the tonotopic axis of the MNTB, consistent with a role for FMRP as a repressor of protein translation. It will be important to determine the basis for the FMRP-dependent dysregulation of Kv3.1b translation in *fmr1* KO mice; these future investigations may provide clues to novel approaches towards therapeutic interventions.

Rescue of LTP deficits in the hippocampus from fmr1 KO mice by a Kv4 channel blocker

As mentioned earlier, deficits in LTP have been reported in the *fmr1* KO mice [63*, 64*, 65], however MPEP fails to correct this deficit in LTP [66, 67, 46**]. The levels of Kv4.2 that generate the A-type K^+ currents (I_A) on the dendritic membrane are critical for synaptic plasticity [87]; loss of Kv4.2 function causes enhanced induction of LTP in hippocampal CA1 pyramidal neurons [88], while increasing Kv4.2 expression abolishes the ability to induce LTP [89*].

Kv4.2 mRNA has been identified and validated as a binding target for FMRP [43**, 72**]. Kv4.2 is the most abundant isoform of dendritic voltage-gated A-type K^+ channel in CA1 pyramidal neurons in the hippocampus [88]. Enriched on the spines of CA1 pyramidal neurons, Kv4.2 is under the regulation of synaptic activity and it in turn contributes to the regulation of synaptic plasticity [87, 89*]. A recent study [43**] found the dendritic localization of Kv4.2 mRNA and FMRP suppression of Kv4.2 levels through the interaction with segments of Kv4.2-3'UTR with U-rich sequences (Figure 1c). Moreover, the deficit in

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LTP induction can be rescued by reducing Kv4 channel activity in hippocampal slices from *fmr1* KO mice [43**] (Figure 1c).

The *N*-methyl-D-aspartate receptor (NMDAR)-induced total protein synthesis is defective in synaptosomes from *fmr1* KO mice [90]. Given the bidirectional feedback regulation between Kv4.2 and NMDAR for the dynamic modulation of synaptic plasticity [89*] and the NMDAR-dependent regulation of dendritic Kv4.2 for branch strength potentiation [91], it is of interest to determine how the Kv4.2 protein level can recover quickly after its down regulation by NMDAR via internalization and degradation [92-94]. Lee et al. [43**] found that NMDAR activation increases Kv4.2 protein production in an FMRP-dependent process likely involving PP1-dependent dephosphorylation of FMRP, and the resulting de-repression of Kv4.2 corresponds to a homeostasis mechanism to reset the neuronal activity (Figure 1c).

Taken together, this study identifies Kv4.2 mRNA as a new target of FMRP. Whereas FMRP suppresses Kv4.2 in the basal condition, FMRP suppression is relieved by its dephosphorylation upon NMDAR activation. This derepression to increase Kv4.2 production compensates for NMDAR-mediated Kv4.2 degradation so that there is a transient down regulation of Kv4.2 – a positive feedback regulation of neuronal excitability, thereby maintaining neurons within the dynamic range of synaptic plasticity. Given that a Kv4 channel blocker (the cysteine knot venom peptide; heteropodatoxin HpTx2) rescues the LTP deficit in *fmr1* KO mice, pharmacological inhibitors of Kv4.2 may be considered for potential therapeutic applications.

Therapeutic prospects

FXS symptoms likely involve multiple neuronal signaling pathways in different brain regions, including those linked to mGluR and several potassium channels that have been recently identified as novel therapeutic targets for treating FXS. A major focus of the field is to determine which pathways are crucial for the symptoms observed in patients and which of these are amenable to pharmaceutical intervention. These molecular studies of FMRP have led to the rational design of novel therapeutics. Now that the identities of many FMRP targets are known, investigators may be able to associate the dysregulation of specific target mRNAs with specific FXS phenotypes. In light of the significant variability of the disease and the limitations of mGluR drug therapy, patients with the disorder could potentially benefit from a cocktail of drugs.

Given that potassium channels (Slack, Kv3.1b and Kv4.2) show alterations in their activity or expression levels in *fmr1* KO mice, modulators have therapeutic potentials in fragile X treatments. Potassium channel openers have been suggested for countering or preventing neuronal damages by interfering with different steps of the neurodegenerative cascade [95]. Thus, the discovery and development of pharmaceutical drugs targeting potassium channels is important for treating a variety of medical conditions and diseases. Recent advances in large-scale screening for molecules affecting ion channel function using optical-based and electrophysiological technologies have improved drug development in this field [96]. Moreover, methods for the discovery of peptide-based neurotoxins and other natural products have proven useful not only in the pharmacological assessment of ion channel structure and function, but also in the identification of lead molecules for drug development [96]. The extensive efforts and experience in developing pharmacological reagents targeting ion channels followed by a suitable validation process should facilitate the development of therapeutic reagents for consideration of potential FXS treatment.

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Highlights

- FXS is a common form of mental disability and one of the known causes of autism.
- Targeted treatments of FXS based-on the mGluR theory is a feasible therapeutic strategy.
- It is also important to extend our understanding of FMRP functions beyond mGluR signaling.
- Several potassium channels show alterations in mouse models of FXS.
- We suggest possible therapeutic avenues for treating FXS regarding the role of potassium channels

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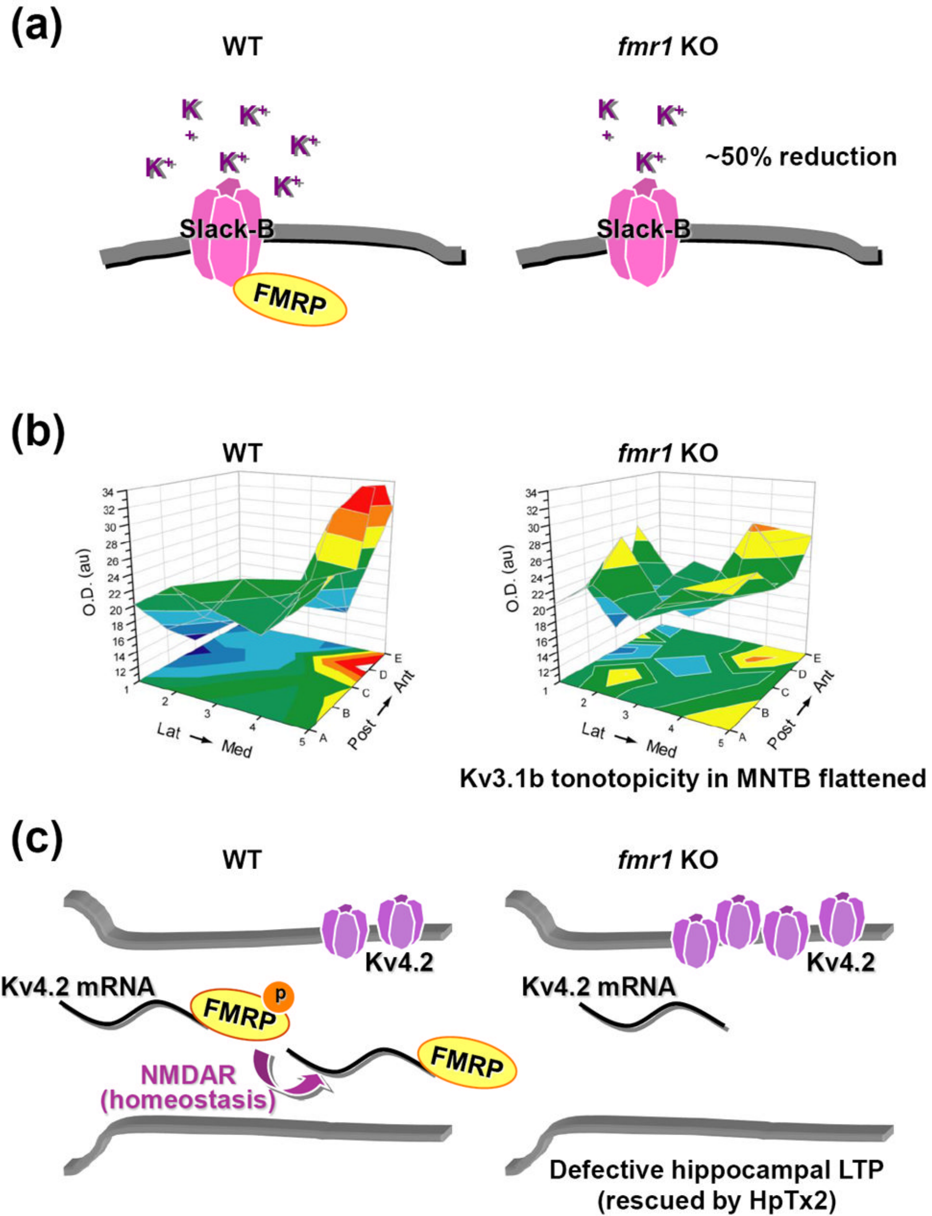

Figure 1.

Summary of the alterations of potassium channels in *fmr1* KO mice.

(a) FMRP increases Slack-B channel activity by binding to the C-terminus of Slack-B. Slack potassium currents are reduced by about 50% in *fmr1* KO mice.

(b) While WT animals show a tonotopic gradient of Kv3.1b expression in the MNTB, *fmr1* KO mice display dramatically flattened gradients. Representative three-dimensional plots of the average Kv3.1b immunoreactivity (OD) in each of 25 stereotaxic zones. Lat, lateral; Med, medial; Post, posterior; Ant, anterior. (Adapted from [78**].)

(c) FMRP suppression of Kv4.2 levels in neuronal dendrites through its interaction with segments of Kv4.2-3'UTR. Whereas FMRP suppresses Kv4.2 in the basal condition, FMRP suppression is relieved by its dephosphorylation upon NMDAR activation, as a homeostasis mechanism to reset the neuronal activity. Without FMRP, the basal level of Kv4.2 is

elevated in *fmr1* KO mice. Reducing Kv4 channel activity by the specific channel blocker HpTx2 rescues the deficits of LTP induction in the hippocampus from *fmr1* KO mice.

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