The mGluR theory of fragile X mental retardation

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Many of the diverse functional consequences of activating group 1 metabotropic glutamate receptors require translation of pre-existing mRNA near synapses. One of these consequences is long-term depression (LTD) of transmission at hippocampal synapses. Loss of fragile X mental retardation protein (FMRP), the defect responsible for fragile X syndrome in humans, increases LTD in mouse hippocampus. This finding is consistent with the growing evidence that FMRP normally functions as a repressor of translation of specific mRNAs. Here we present a theory that can account for diverse neurological and psychiatric aspects of fragile X syndrome, based on the assumption that many of the protein-synthesis-dependent functions of metabotropic receptors are exaggerated in fragile X syndrome. The theory suggests new directions for basic research as well as novel therapeutic approaches for the treatment of humans with fragile X, the most frequent inherited cause of mental retardation and an identified cause of autism.

Fragile X is the most common inherited form of human mental retardation. It is typically caused by a trinucleotide repeat expansion in the X-linked FMR1 gene that prevents expression of the encoded protein, called fragile X mental retardation protein (FMRP) [1]. Brain development in the absence of FMRP gives rise to the major symptoms of fragile X syndrome in humans [2,3]. These include mental retardation in the moderate to severe range, attention deficit and hyperactivity, anxiety with mood lability, and obsessive—compulsive and autistic behaviors. People with fragile X also have poor motor coordination, and an increased incidence of epilepsy. Common peripheral symptoms are heightened sensitivity to tactile irritation and loose bowel movements. Non-neurological symptoms can include a long face, large ears, hyperextensible joints, and enlarged testes in post-pubescent males. Autopsy studies indicate that although the brain is grossly normal, dendritic spines are longer and immature in appearance [4–6]. Spine abnormalities have long been associated with human mental retardation of unknown etiology [7], as well as with Down’s and Rett syndromes [8]. Spines, of course, are where excitatory synaptic transmission and several important forms of synaptic plasticity occur.

A key advance for understanding fragile X was the isolation of the FMR1 gene and subsequent generation of the Fmr1 knockout mouse [9]. The phenotype of the Fmr1 knockout mouse is multifaceted, and generally consistent with the human [3]. The most robust and reproducible behavioral phenotypes are increased locomotor activity and reduced habituation in an open field, and increased susceptibility to audiogenic seizure. Additionally, mild learning deficits have been noted [10]. Importantly, the Fmr1 knockout has dendritic abnormalities analogous to those in humans—more long, thin spines [11,12]. Thus, there is reason to suspect that many aspects of fragile X can be attributed to altered synaptic development and plasticity.

A study of synaptic plasticity in the hippocampus of the Fmr1 knockout mouse suggested a novel connection between metabotropic glutamate receptor (mGluR) signaling and the fragile X phenotype [13]. The resulting theory has generated some excitement in the fragile X field because it points to a possible therapeutic approach to the disorder. Here we articulate the origins, assumptions, and potential consequences of the ‘mGluR theory’. This is a case study in how basic research can lead in unexpected directions.

**From long-term synaptic depression to fragile X**

Synaptic activity in the brain can trigger long-lasting changes in synaptic strength called long-term potentiation (LTP) and long-term depression (LTD). In neonates, the mechanisms of LTP seem to be important for retaining nascent synapses, whereas LTD mechanisms seem to be important for activity-guided synapse elimination. These same mechanisms, working in concert, contribute to learning and memory storage throughout postnatal life [14].

Understanding the mechanisms and functional significance of LTP and LTD first required the establishment of paradigms in which they can be reliably elicited. In the case of LTD, the first useful model was developed by Ito in the cerebellar cortex [15,16]. For many years it was believed that homosynaptic LTD might be the exclusive province of the cerebellum, where it was specialized for motor learning, coordination, and balance. However, a reliable method for inducing LTD using low-frequency
synaptic stimulation was eventually established in hippocampus [17], and the study of LTD at synapses throughout the brain has subsequently flourished.

LTD of the parallel fiber to Purkinje cell synapse in the cerebellum is elicited by coincident activation of the parallel fibers and the climbing fibers. Climbing fiber synapses are very powerful, and their activation leads to a large rise in intracellular calcium that is permissive for LTD. However, a key signal that distinguishes active from inactive parallel fiber synapses, and which is required to trigger LTD, is activation of postsynaptic group 1 (Gp1) mGluRs. Gp1 mGluRs, by definition, stimulate phosphoinositide hydrolysis and comprise mGluR1 and mGluR5, which have different tissue and subcellular localization. Induction of cerebellar LTD requires activation of mGluR1 [18,19].

Although the most thoroughly characterized form of LTD in the hippocampus is triggered by activation of postsynaptic NMDA receptors, there is evidence for a second type of LTD that, like in cerebellum, requires activation of postsynaptic Gp1 mGluRs [20]. Interestingly, although both forms of hippocampal LTD can be induced by identical patterns of synaptic stimulation [21,22] and can be expressed as a decrease in the number of postsynaptic AMPA receptors [23,24], they are mechanistically distinct. One of the important distinctions is that LTD triggered by mGluR activation (mGluR-LTD) requires the rapid translation of preexisting mRNA in the postsynaptic dendrites [25]. Although NMDA-receptor-dependent LTD, like LTP, also requires protein synthesis to persist longer than a few hours [26,27], the early expression is protein-synthesis-independent [25,27]. Another distinction is that whereas NMDA-receptor-dependent LTD is readily reversible, mGluR-dependent LTD is not [20]. An irreversible loss of glutamate receptors during mGluR-LTD could be a prelude to synapse elimination [24].

The LTD literature can be confusing because different routes of induction can engage different mechanisms, and these can vary with age and synapse type; so it is important for us to be explicit. Although many details remain to be worked out, particularly the precise role for protein synthesis, the mGluR-LTD in area CA1 that we describe here requires activation of mGluR5 (the major postsynaptic Gp1 receptor in the forebrain) [28], the G₄ family of G-proteins [29], and extracellular signal-regulated kinase (ERK), one of the mitogen-activated protein kinases (MAPK) [30]. Although the depression of synaptic transmission and the loss of surface-expressed glutamate receptors occur immediately after mGluR5 activation without new protein synthesis, these changes rapidly revert (within 30 min) if postsynaptic mRNA translation is inhibited (Figure 1a,b). However, new protein synthesis is only required for a finite critical period (<60 min) immediately after activation of mGluRs. A model that captures these features of mGluR-LTD is presented in Figure 1c).

There were several reasons why it was of interest to investigate the role of FMRP in protein-synthesis-dependent mGluR-LTD. FMRP mRNA is found in dendrites and FMRP protein binds mRNA [31], as we will discuss further. However, the strongest rationale for studying FMRP in
LTD was that activation of Gp1 mGluRs was reported to stimulate the synthesis of this protein rapidly in synapses [32]. We therefore investigated mGluR-LTD in the Fmr1 knockout mouse. The anticipated phenotype was defective LTD, so it came as a surprise that mGluR-LTD was actually significantly enhanced in the mutants as compared to wild-type littermates [13]. By contrast, there were no differences in NMDA-receptor-dependent LTD (at least not in the early, protein-synthesis-independent phase), consistent with earlier studies that failed to find any deficits in NMDA-receptor-dependent LTP [33,34]. Thus, the phenotype was specific to the mGluR-dependent form of synaptic plasticity.

Our data showed that one functional consequence of Gp1 mGluR activation – protein-synthesis-dependent LTD – was exaggerated in the absence of FMRP. Based on the evidence that FMRP is normally synthesized following stimulation of Gp1 mGluRs, we proposed a simple model to account for our findings (Figure 2a). According to this model, mGluR activation normally stimulates synthesis of proteins involved in stabilization of LTD and, in addition, FMRP. The FMRP functions to inhibit further synthesis (an example of end-product inhibition), and puts a brake on LTD. Recent research suggests that this ‘black box’ model is actually consistent with the biology of FMRP.

Emerging functions of FMRP

FMRP has been the subject of several recent reviews [3,35–37]. The excitement stems in part from the fact that fragile X syndrome is caused by a defect in a single gene, so understanding the function of the missing protein promises to provide insight into the pathophysiology of mental retardation, as well as cognition in general. However, the other reason for sudden interest is that FMRP has proven to be a fascinating molecule; it has captured the attention of neurobiologists interested in the synaptic control of protein synthesis, and the role of protein synthesis in changing synaptic structure and function.

Of particular importance for our thesis is the role of FMRP in mRNA translation regulation. FMRP is associated with actively translating polysomes in an RNA-dependent manner via messenger ribonucleoprotein (mRNP) particles [38]. A missense mutation (I304N) in the RNA-binding domain of the protein prevents the polysome association and results in severe mental retardation, suggesting that this interaction is key to the function of the protein [39]. Several innovative approaches have been taken to identify the mRNA targets of FMRP, in the hope of identifying which proteins are misregulated in fragile X [40–43]. This story has taken a very interesting twist recently with the discovery that FMRP specificity can be conferred by binding RNAs that are untranslatable. In one recent study, FMRP was shown to bind BC1 [44], an untranslated message abundant in dendrites that functions as a translation repressor [45]. It was reported that BC1 can specifically repress translation of the mRNAs for the synaptic proteins Arc and α-CaMKII, and the dendritic microtubule-associated protein 1b (MAP1b) [44]. Furthermore, FMRP has been shown to be a part of the machinery for translation regulation by RNA interference (RNAi) [46]. Specifically, FMRP is part of a RISC nuclease complex that represses translation by directing small interfering RNAs (siRNA) to their mRNA targets [47,48].

The case for FMRP as a translational repressor seems particularly strong for MAP1b. First, genetic evidence in

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Models of protein synthesis-dependent, functional and structural consequences of group 1 (Gp1) metabotropic glutamate receptor (mGluR) activation at hippocampal synapses, and the role of FMRP. (a) Model to account for exaggerated mGluR-long-term depression (mGluR-LTD) in the Fmr1 knockout mouse, based on the assumption that the fragile X mental retardation protein (FMRP) is synthesized in response to mGluR activation and functions as a translational repressor (modified from Ref. [13]). (b) Model relating the net loss of synaptic AMPA and NMDA receptors [24] and elongation of dendritic spines [67] observed following Gp1 mGluR activation in cultured hippocampal neurons. We propose that these responses are indicative of increased synapse loss and/or turnover following Gp1 mGluR activation. Both responses require mRNA translation and, if exaggerated in the absence of FMRP, could account for the delay in synaptic maturation and elongated spines in fragile X. According to this view, elongated spines in fragile X are weakened synapses on route to elimination, and/or filopodial extensions of dendrites seeking to replace lost synapses.
flies in vivo shows that the Drosophila FMRP homolog (DFXR) represses translation of Futsch, ortholog of the mammalian MAP1b [49]. Second, although anatomical variation has been noted [43], the protein is significantly increased in total brain lysates from Fmr1 knockout mice [44]. Third, MAP1b mRNA is increased on polysomes in cells derived from fragile X patients, consistent with FMRP negatively regulating translation of this transcript [40]. Finally, the absence of FMRP has recently been shown to directly interfere with the developmentally programmed MAP1b decline in the mammalian brain, with the increased MAP1b leading to increased microtubule stability (Y. Feng et al., unpublished).

Experiments in vitro initially suggested the possibility that FMRP is a general repressor of translation [50,51]. However, there are now several studies suggesting this role might be restricted to specific messages. Indeed, synthesis and/or subcellular localization of several proteins appears to be disrupted in the absence of FMRP [42,43,52]. We will return to this point later in the review.

Emerging functions of Gp1 mGluR-stimulated protein synthesis

It has been recognized for many years that the machinery for protein synthesis is present in the dendrites of cortical neurons near synapses [53,54]. Translation of pre-existing mRNAs can be activated in different ways by different signals (e.g. TrkB and NMDA receptor activation), but it is now very clear that activation of Gp1 mGluRs is a potent stimulus for local protein synthesis [52,55,56]. Moreover, in cases where it has been specifically examined, many functional consequences of Gp1 mGluR activation are – like LTD – protein-synthesis-dependent (Table 1).

The first study to show that a lasting effect of Gp1 mGluR activation requires protein synthesis was performed by Merlin et al. using hippocampal slices. The phenomenon under investigation was the gradual and persistent prolongation of epileptiform bursts in area CA3 following activation of Gp1 mGluRs with the selective agonist (R,S)-3,5-dihydroxyphenylglycine (DHPG). This action of DHPG on network excitability was blocked by inhibitors of mRNA translation, but not transcription [57–59].

In hippocampal area CA1, brief activation of Gp1 mGluRs can facilitate the induction of LTP without altering baseline responses [60]. However, stronger activation of Gp1 mGluRs can reverse previously induced LTP [61] and, as reviewed above, induce LTD de novo [20,62]. All these effects are blocked by protein synthesis inhibitors [25,63,64].

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Our studies in the Fmr1 knockout mouse led us to suggest that exaggerated LTD could slow net synaptic maturation (by tipping the balance away from synapse gain towards synapse loss during the critical period of synaptogenesis), and therefore contribute to the developmental delay and cognitive impairment associated with fragile X (Figure 2b). However, FMRP is widely expressed in the brain, including most, if not all, neurons that express Gp1 mGluRs. We therefore considered the possibility that all functional consequences of Gp1 mGluR-dependent protein synthesis might be exaggerated in the absence of FMRP. An intriguing picture began to emerge. From the literature already reviewed here, overactive or inappropriate Gp1 mGluR signaling might lead to epilepsy, cognitive impairment, developmental delay, an increased density of long, thin dendritic spines, and loss of motor coordination – key features of fragile X syndrome (Table 1).

The picture becomes even more complete when we consider other functions of Gp1 mGluRs not yet tied to protein synthesis. Suspicious coincidences include the following:

- Fear memory formation and LTP in amygdala are mGluR5-dependent [72], and mGluR5 antagonists are anxiolytic [73]. Anxiety and autistic behavior are common in fragile X, and the Fmr1 knockout mice display abnormal contextual and conditional fear responses [34].

Table 1. The functional consequences of Gp1 mGluR activation that have been shown to require mRNA translation, listed in the order in which they were discovered, and their possible relevance to fragile X syndrome

<table>
<thead>
<tr>
<th>Effect of Gp1 mGluR-stimulated protein synthesis</th>
<th>Related fragile X phenotype in mouse or human</th>
<th>Refs</th>
</tr>
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<tbody>
<tr>
<td>Prolongation of epileptiform bursts in hippocampal area CA3</td>
<td>Childhood epilepsy (human)</td>
<td>[57,59]</td>
</tr>
<tr>
<td>Priming of LTP in hippocampal area CA1</td>
<td>Audiogenic seizure (mouse)</td>
<td></td>
</tr>
<tr>
<td>LTD in hippocampal area CA1</td>
<td>Cognitive impairment, developmental delay</td>
<td>[63]</td>
</tr>
<tr>
<td>Internalization of postsynaptic glutamate receptors on cultured hippocampal neurons</td>
<td>Cognitive impairment, developmental delay</td>
<td>[24]</td>
</tr>
<tr>
<td>LTD in cerebellar cortex</td>
<td>Loss of motor coordination</td>
<td>[71]</td>
</tr>
<tr>
<td>Elongation of dendritic spines on cultured hippocampal neurons</td>
<td>Elongated, immature dendritic spines</td>
<td>[67]</td>
</tr>
<tr>
<td>Reversal of LTP (depotentiation) in hippocampal area CA1</td>
<td>Cognitive impairment, developmental delay</td>
<td>[64]</td>
</tr>
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*Abbreviations: Gp1 mGluR, group 1 metabotropic glutamate receptor; LTD, long-term depression; LTP, long-term potentiation.
• LTP of the corticostriatal synapse, believed to be important for habit formation [74], requires activation of mGluR1 and mGluR5 [75]. Fragile X syndrome is characterized by obsessive–compulsive behaviors.

• The mGluR5-specific antagonist 2-methyl-6-phenylethynyl-pyridine (MPEP) is anticonvulsant, and raises the threshold for audiogenic seizure in sensitive strains of mice [76]. Enhanced sensitivity to audiogenic seizures is a robust phenotype in Fmr1 knockout mice in several genetic backgrounds [77].

• mGluR5 activation induces a long-term increase in the excitability of neocortical layer 5 neurons [78]. Fragile X is characterized by heightened behavioral responses to sensory stimuli, and larger sensory evoked potentials [79].

• mGluR1 and mGluR5 knockout mice show impaired pre-pulse inhibition of auditory startle [80]. Pre-pulse inhibition is enhanced in Fmr1 knockouts [77,81].

• mGluR5 is expressed in C-fiber innervation of the skin [82] where it has been implicated in the mechanisms of hyperalgesia [83,84]. Individuals with fragile X exhibit heightened sensitivity to tactile irritation.

• mGluR5 is expressed in the enteric innervation of the ileum [85,86]. Agonists promote, and antagonists slow, intestinal mobility. Loose bowels are a common complaint in fragile X.

• Translation of the circadian rhythmicity of the molecular clock in the mouse suprachiasmatic nucleus into neural firing requires activation of Gp1 mGluRs [87]. Disrupted circadian rhythm is a striking phenotype in Drosophila lacking dFMR [88–90].

Putting these pieces together, it appeared that over-active signaling by group 1 mGluRs could contribute to many of the symptoms of fragile X, not just exaggerated LTD and slowed synaptic development. This synthesis suggested a theory – the psychiatric and neurological aspects of fragile X syndrome are a consequence of exaggerated responses to mGluR1/5 activation – that was based on the following assumptions:

(i) Proteins are synthesized in response to activation of mGluR1/5 near synapses in many brain regions, where they contribute to diverse neuronal functions.

(ii) FMRP negatively regulates responses triggered by mGluR-stimulated protein synthesis.

This theory, portrayed in Figure 3(a), was first presented to a collection of experts at a Cold Spring Harbor Laboratory Banbury Meeting in April 2002.

Predictions and progress
A theory can be tested in two ways: (i) assessing the validity of the underlying assumptions, and (ii) spinning out their consequences [91]. The follow-up Banbury meeting in 2003 revealed that such tests are underway in several laboratories, in addition to our own. It is premature to report on these studies, but we can make some explicit predictions.

The first assumption suggests that many of the long-lasting responses to Gp1 mGluR activation will prove to be protein synthesis dependent. In the case of cerebellar LTD, this assumption was tested and validated [71]. We predict that Gp1 mGluR-dependent corticostriatal and amygdala LTP share this requirement for rapid mRNA translation (without new transcription). We also speculate that experience-dependent priming of audiogenic seizures will prove to be an mGluR5- and protein-synthesis-dependent form of synaptic or cellular plasticity.

A prediction that derives from the second assumption is that other known consequences of Gp1 mGluR-dependent protein synthesis will be exaggerated in the Fmr1 knockout mouse. These should include increased cerebellar LTD, prolonged epileptiform bursts in hippocampal area CA3, and greater LTD priming and depotentiation in area CA1, and we expect that new behavioral phenotypes could emerge based on these findings. We also predict a greater response to DHPG in cultured hippocampal neurons – longer, thinner spines and an exaggerated loss of glutamate receptors. It is noteworthy that a paper recently appeared showing that one biochemical consequence of Gp1 mGluR activation, de novo synthesis of the synaptic protein PSD95, fails to occur in cultured cortical neurons from the Fmr1 knockout mouse [52]. Thus, in future iterations of the theory, more precision will be required in specifying the protein-synthesis-dependent responses negatively regulated by FMRP (see following discussion).

The most important consequence of the theory, obviously, is that aspects of the fragile X phenotype should be rescued by reducing signaling through Gp1 mGluRs. Partial rescue might be accomplished genetically, for example, by crossing the Fmr1 knockout mice with mice
lacking one or both genes for mGluR5 and mGluR1. Although less definitive, an even more exciting possibility is pharmacological rescue, for example, with Gp1 mGluR antagonists. First indications are positive: very recent data from Bauchwitz and colleagues indicates that the robust audiogenic seizure phenotype in Fmr1 knockout mice is prevented by systemic administration of the mGluR5 antagonist MPEP [92].

Prospects for treatment of fragile X syndrome with Gp1 mGluR antagonists

The theory portrayed in Figure 3(a) suggests that it might be possible to overcome the loss of FMRP by dampening the protein synthesis triggered by activation of Gp1 mGluRs – this is the conceptual basis for the use of mGluR antagonists to reverse the fragile X phenotype. However, two caveats must be considered. First, as mentioned previously, recent research suggests that although some proteins are overexpressed in the absence of FMRP (e.g. Arc and MAP1b) [44], others appear to be under-expressed or misexpressed [42,43,52]. A revision of our model to account for these recent findings is shown in Figure 3(b). According to this scheme, mGluR activation stimulates the translation of two pools of mRNA, those that are negatively regulated by FMRP (pool I) and those that are not (pool II). Competition between the pools for the translation machinery leads to a yin–yang, or push–pull, type of regulation. By inhibiting translation of messages in pool I, FMRP promotes translation of messages in pool II. Conversely, in the absence of FMRP increased translation of pool I inhibits translation of pool II. Such a model might be a better fit to available data, but it does raise concern about the quality of mGluRs as a target for treatment of fragile X. If aspects of the fragile X phenotype are attributable to decreased translation of mGluR-stimulated synthesis of proteins in pool II, it is difficult to see how an mGluR antagonist would be useful (selective blockers of pool I translation would be an alternative). The second (possibly related) caveat is that animals lacking mGluR5 [93] show cognitive deficits. Thus, blocking mGluR5 could potentially exacerbate the cognitive impairments in fragile X.

Despite these potential concerns, the known actions of Gp1 mGluR antagonists clearly suggest considerable therapeutic potential in fragile X. Most attention has been directed to mGluR5 antagonists, because mGluR1 blockers cause ataxia by disrupting cerebellar function. The prototypical mGluR5-selective antagonist is MPEP [94]. In animal models, systemically administered MPEP has been shown to have broad and potent anticonvulsant and anxiolytic actions without causing overt effects on locomotor activity. MPEP can reverse inflammation-induced mechanical hyperalgesia by inhibiting mGluR5 receptors in the C-fibers of the skin. And, by inhibiting mGluR5 receptors in the gut, MPEP can reduce bowel motility. Even the most skeptical would agree it is astonishing that a single compound could target such disparate symptoms of human fragile X syndrome as epilepsy, anxiety, hyperalgesia, and loose bowels.

As for the first caveat raised above, it is possible that we are correct about the utility of mGluR5 antagonists in fragile X for the wrong reasons, or this concern might simply be unwarranted. Regarding the second caveat, proper cognitive function appears to require synaptic plasticity within a finite dynamic range. Mutations that cause this range to be exceeded in either direction (e.g. by too much or too little LTP) impair learning and memory [95]. Antagonists of mGluR5 might correct the mild cognitive deficits seen in the Fmr1 knockout by bringing synaptic plasticity back into its proper range. Thus, two wrongs (cognitive impairment in Fmr1 and mGluR5 knockout mice) could make a right.

We believe mGluR5 antagonists have great promise as a potential treatment for the neurological and psychiatric symptoms of fragile X expressed in adults. However, if the syndrome is a lasting consequence of brain development with exaggerated Gp1 mGluR signaling, it is possible that early intervention with receptor antagonists could prevent some symptoms from occurring altogether.

Beyond fragile X

There is a great deal left to be learned about how protein synthesis is regulated by, and in turn influences, synaptic transmission in the brain. However, two things are certain: (i) FMRP is only one of many proteins and signaling pathways involved in the synaptic regulation of protein synthesis, and (ii) where there is biology, there is pathology. If we are correct that key aspects of fragile X are due to unregulated synaptic protein synthesis, it seems reasonable to anticipate that other disorders with similar symptoms might be traced to defects elsewhere in the same molecular pathways. It is interesting to note that other types of human developmental disorder, including autism, have many of the same core characteristics as fragile X. These include developmental delay and cognitive impairment, increased incidence of childhood epilepsy, a higher proportion of long, thin dendritic spines, reduced motor coordination, heightened anxiety, and altered gastrointestinal function. Thus, the mGluR theory could have broader applicability than just to fragile X.

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