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Review

Therapeutic implications of the mGluR theory of fragile X mental retardation

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Evidence is reviewed that the consequences of group 1 metabotropic glutamate receptor (Gp1 mGluR) activation are exaggerated in the absence of the fragile X mental retardation protein, likely reflecting altered dendritic protein synthesis. Abnormal mGluR signaling could be responsible for remarkably diverse psychiatric and neurological symptoms in fragile X syndrome, including delayed cognitive development, seizures, anxiety, movement disorders and obesity.

Keywords: Anxiety disorder, autism, cognitive development, dendritic protein synthesis, long-term depression, metabotropic glutamate receptors, seizure disorder

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Neuroscientists have long been fascinated by the observation that polyribosomes and the molecular machinery of protein synthesis are localized near dendritic spines, major sites of excitatory synaptic transmission and plasticity (Steward & Schuman 2001). Glutamate is the neurotransmitter at most excitatory synapses in the brain, and there is now considerable evidence that activation of group 1 metabotropic glutamate receptors (Gp1 mGluRs, comprised of mGluR1 and mGluR5) is a potent stimulus for protein synthesis (Job & Eberwine 2001; Shin *et al*. 2004; Todd *et al*. 2003; Weiler & Greenough 1993). Moreover, in cases where it has been specifically examined, many of the lasting functional consequences of Gp1 mGluR activation have been found to be dependent on mRNA translation, but not transcription (Huber *et al*. 2000; Karachot *et al*. 2001; Lee *et al*. 2002; Merlin *et al*. 1998; Raymond *et al*. 2000; Snyder *et al*. 2001; Stoop *et al*. 2003; Vanderklish & Edelman 2002; Zho *et al*. 2002). Other than the common requirement for protein synthesis, however, the precise consequence of activating Gp1 mGluRs varies widely, depending on the neuron and the circuit in which it resides (Fig. 1). Systemic activation or inhibition of Gp1 mGluR-mediated protein synthesis by genetic or pharmacological means therefore would be expected to have diverse effects.

The fragile X mental retardation protein (FMRP) has attracted considerable interest as a potential regulator of dendritic protein synthesis. However, the picture emerging from recent biochemical and cell biological studies is confusing and, at times, contradictory. The fragile X mental retardation protein is contained within ribonucleoprotein granules that traffic specific mRNAs (including *Fmr1*) to sites of synaptic transmission. Activation of Gp1 mGluRs on cultured hippocampal neurons with the selective agonist (R,S)-3,5-dihydroxyphenylglycine (DHPG) triggers the delivery of FMRP to dendrites (Antar *et al*. 2004). In cultured cortical neurons, expression of both the FMRP and the synaptic protein PSD-95 is increased after activating Gp1 mGluRs. However, DHPG treatment fails to increase PSD-95 levels in cultures prepared from *Fmr1* knockout (KO) mice lacking FMRP (Todd *et al*. 2003). Similarly, DHPG fails to stimulate polyribosome assembly in synaptosomes prepared from the cortex of *Fmr1* KO mice (Weiler *et al*. 2004). Together, these data are consistent with the proposal that FMRP is a requirement for dendritic protein synthesis. On the other hand, there is also compelling evidence that synthesis of some proteins (e.g. MAP1b) is repressed by FMRP and that this repression is relieved in the *Fmr1* KO and in humans with fragile X (reviewed by Bear *et al*. 2004; see also Warren article, this issue). The disparate findings may be related to differences in the tissue, the preparation, the mRNA and the subcellular compartment under investigation (Miyashiro & Eberwine 2004).

Several years ago, we asked the simple question of how a functional consequence of Gp1 mGluR activation differs in the *Fmr1* KO mouse. The physiological response under investigation was a form of synaptic plasticity, long-term depression (LTD), that is triggered in the CA1 region of hippocampus by appropriate stimulation of mGluR5. In previous studies, we had shown that this type of LTD is protein-synthesis dependent (Huber *et al*. 2000) and expressed, in part, by internalization of glutamate receptors (Snyder *et al*.

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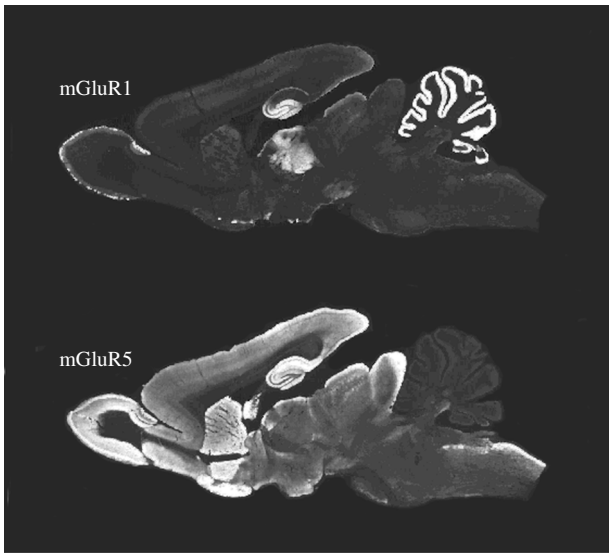

Figure 1: Distribution of group 1 metabotropic glutamate receptor (Gp1 mGluR) protein in the rat brain (modified from Shigemoto & Mizuno 2000).

2001). In the *Fmr1* KO mice, we discovered that mGluR-induced LTD was increased in the hippocampus (Huber *et al*. 2002). These findings are consistent with the hypothesis that FMRP normally represses the protein synthesis required for stable expression of mGluR-dependent LTD – in the absence of repression, we see more LTD in the KO mice. Regardless of the specific mechanism involved, however, the data clearly showed that one functional consequence of mGluR activation is exaggerated in the absence of the fragile X protein.

We next wondered whether all functional consequences of mGluR-dependent protein synthesis might be exaggerated and, if so, whether this could account for aspects of the phenotype in fragile X. The picture that emerged was remarkable and led us to propose the 'mGluR theory' of fragile X (Bear *et al*. 2004). The theory is based on two assumptions that: (1) many lasting consequences of Gp1 mGluR activation require protein synthesis and (2) these are exaggerated in the absence of FMRP. Such theories have value if they stimulate research, and it is encouraging to note that the assumptions have been tested and validated in several functional contexts. More importantly, however, the mGluR theory suggests a sound scientific rationale for the treatment of fragile X syndrome. If symptoms of fragile X arise from excessive signaling through Gp1 mGluRs, then it should be possible, in principle, to treat them with drugs that inhibit the receptors and/or the downstream intracellular signals they initiate.

In this brief review, the author illustrates how the mGluR theory offers a clear molecular logic behind a diverse constellation of symptoms associated with fragile X syndrome. The author will also discuss the prospect of treating these symptoms with drugs that inhibit mGluRs.

Cognitive development

Fragile X is characterized by moderate to severe mental retardation (Bakker & Oostra 2003; Hagerman 2002; Hagerman & Hagerman 2002). Cognition is an emergent property of the cerebral cortex, and the trajectory of cognitive development depends on experience-dependent modifications of synaptic connections among cortical neurons. Synaptic excitation in the cortex is mediated by α-amino-3-hydroxy-5-Methyl-4-isoxazolepropionate (AMPA) and N-Methyl-D-asparate (NMDA) receptors (the major classes of glutamate-gated ion channel). It is therefore of interest that a biochemical phenotype in the *Fmr1* KO mouse is the reduced expression of the AMPA receptor subunit protein *Glu*RI in synaptic plasma membranes prepared from frontal cortex (Li *et al*. 2002).

The experience-dependent delivery and removal of AMPA receptors from cortical synapses are essential for normal cortical development as well as for adult learning and memory. A great deal has been learned about the mechanisms responsible for this synaptic plasticity by the study of the experimental phenomena of long-term potentiation (LTP) and LTD (Malenka & Bear 2004). As mentioned in the introduction, one form of LTD is induced in the CA1 region of hippocampus by activation of mGluR5 (Huber *et al*. 2001), the major Gp1 mGluR in the cerebral cortex (Fig. 1). In cultured hippocampal neurons, activation of mGluR5 with DHPG stimulates the loss of AMPA receptors from synapses, and this is believed to model a mechanism used during cortical development to refine synaptic connections (Snyder *et al*. 2001). Both the LTD and the internalization of AMPA receptors are protein-synthesis dependent, and both the responses are increased in neurons from the *Fmr1* KO mouse (Huber *et al*. 2002) (N. Nagarajan and M.F.B, unpublished observations). Excessive mGluR-dependent LTD during the development could explain the loss of AMPA receptor protein in synaptic plasma membranes from the KO mice.

Neurons in the cerebral cortex of mice and humans lacking FMRP also have a greater proportion of long, thin dendritic spines (Hinton *et al*. 1991; Irwin *et al*. 2001; Rudelli *et al*. 1985). Spine abnormalities have long been associated with human mental retardation of unknown etiology (Purpura 1974) as well as with Down's and Rett syndromes (Kaufmann & Moser 2000). This phenotype may also be related to excessive Gp1 mGluR signaling. Vanderklish and Edelman (this issue) found that prolonged treatment of hippocampal neurons with DHPG also increases the proportion of long, thin dendritic spines (Vanderklish & Edelman 2002). These structural changes and LTD are likely to be related, because synapses on thin spines have a smaller postsynaptic density, fewer AMPA receptors and a reduced number of synaptic vesicles docked at the presynaptic active zone (Harris & Stevens 1989; Nusser *et al*. 1998; Schikorski & Stevens 1997).

Taken together, these findings suggest that exaggerated mGluR5 signaling could contribute to the altered trajectory of

cortical development in fragile X. A number of genetic tests of this hypothesis are feasible in mice; for example, by crossing *Fmr1* KO mice with animals deficient in mGluR5. Another approach would be treatment with a drug that blocks mGluR5, such as 2-methyl-6-phenylethynyl-pyridine (MPEP, with the caveat that at high concentrations, it blocks NMDA receptors). An intriguing possibility is that chronic treatment with an mGluR5 antagonist during a critical period of postnatal development could be 'disease modifying' in animals and humans lacking FMRP.

This possibility has received some striking support very recently in studies of the *Drosophila* model for fragile X syndrome. Flies lacking *dfmr1*, the homologue of *FMR1* in humans, display altered courtship behavior, decreased memory in a conditioned courtship assay and alterations in the structure of the brain (the mushroom bodies) (McBride *et al*. in press). Remarkably, McBride, Jongens and colleagues have found that all of these phenotypes in mutant flies are rescued if they are raised with food containing MPEP or several other drugs that are predicted to affect signaling by the *Drosophila* mGluR, *DmGluRA*. The mushroom body defect could only be rescued when drug treatment was begun at the larval stage of development, but significant behavioral rescue occurred even when treatment began in adult flies (McBride *et al*. in press). These remarkable findings have exciting implications for the treatment of human fragile X syndrome. It is interesting to note that one of the effective agents in flies was lithium, which is currently in widespread use in humans for the treatment of mood disorders.

Seizure disorder

A large proportion of humans with fragile X suffer seizures during childhood (Hagerman 1987; Hagerman 2002; Hagerman & Hagerman 2002), and a robust phenotype in the *Fmr1* KO mice is audiogenic seizures. There are compelling connections between excessive Gp1 mGluR activation and epilepsy (Wong *et al*. 2002).

Electroencephalographic measurements reveal two types of synchronized discharge in epilepsy: brief interictal sharp waves with no perceptible behavioral correlate and prolonged ictal bursts, lasting from seconds to minutes, that produce seizures (Zifkin & Cracco 1990). Hippocampal area CA3 has been used to model the mechanisms involved. Bathing a hippocampal slice in drugs that block inhibition leads to the generation of regularly spaced bursts of synchronous activity in CA3 pyramidal cells that resemble interictal sharp waves. These brief bursts will continue for hours *in vitro* without evolving to ictal-like activity. However, ictal-like activity rapidly appears and persists following transient activation of Gp1 mGluRs (Merlin *et al*. 1998). The requirements for this lasting consequence of mGluR activation are strikingly similar to those for LTD. Induction of ictal-like activity requires activation of extracellular signal-regulated kinase (ERK), a subclass of the mitogen-activated protein kinases (Zhao *et al*. 2004), and mRNA translation but not transcription (Merlin *et al*. 1998).

A prediction of the mGluR theory of fragile X is that this protein-synthesis-dependent response to mGluR activation, like LTD, should be exaggerated in the absence of FMRP. Recently, Wong and colleagues reported a test of this prediction (S. Chuang, Q. Yan, R.P. Bauchwitz, R.K.S. Wong. Program no. 228.5. *2004 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience 2004. Online). They found that ictal-like activity emerged spontaneously in slices from the *Fmr1* KO mouse and that this could be reversed by administering the mGluR5 antagonist MPEP. Thus, in slices from the mutant (but not wild-type), the endogenous activation of mGluR5 by synaptically released glutamate was sufficient to trigger the protein synthesis required for the establishment of ictal-like epileptiform activity. This finding supports a key assumption of the mGluR theory.

Antagonists of mGluR5 have previously been shown to have broad anticonvulsant actions (Spooren *et al*. 2001). These include the prevention of audiogenic seizures in sensitive strains of mice. Recent data from Bauchwitz and colleagues indicate that the robust audiogenic seizure phenotype in *Fmr1* KO mice is also prevented by systemic administration of the mGluR5 antagonist MPEP (R.P. Bauchwitz, Q. Yan, M. Rammal. Program no. 583.20. *2004 Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience 2004. Online). Together, the data suggest that mGluR5 antagonists might selectively target the cause of seizures in fragile X syndrome.

Anxiety disorder

Sensory hyperarousal and anxiety are the *sine qua non* of fragile X syndrome in humans (Hagerman & Hagerman 2002). The biological bases of anxiety disorders are poorly understood, but much attention is focused on the control of the hypothalamic-pituitary-adrenal axis by the amygdala. The amygdala is critical for the expression of learned fear. For example, repeated pairing of an auditory stimulus (a tone) with a footshock causes the animal to exhibit fear in response to the tone alone. There is evidence that the tone–shock pairing induces LTP of the synapses bringing the auditory information to the lateral amygdala (Maren & Quirk 2004). Long-term potentiation in the lateral amygdala requires activation of mGluR5 (Rodrigues *et al*. 2002; Rodrigues *et al*. 2004). A clear prediction deriving from the mGluR theory is that this mechanism of LTP will be dependent on translation of pre-existing mRNA and will be enhanced in the *Fmr1* KO mouse. These predictions remain to be tested.

However, there is already extensive evidence that mGluR5 antagonists are highly effective anxiolytics. According to a

recent review of the evidence by Spooren and Gasparini 2004, mGluR5 antagonists exhibit the widest and the most robust anxiolytic activity in preclinical models seen to date. The effects are comparable to those of benzodiazepines with less sedative activity. Thus, although the site(s) and mechanism(s) of action remain to be determined, there is good reason to believe that mGluR5 antagonists will have therapeutic potential for anxiety in fragile X.

Disorders of movement

Two disorders of movement are common in fragile X syndrome: unco-ordinated voluntary movements and repetitive, obsessive-compulsive-like behaviors (Hagerman & Hagerman 2002). Group 1 metabotropic glutamate receptors are highly expressed in two motor-control structures that might contribute to these symptoms: the cerebellum and the striatum (Fig. 1).

Theories of cerebellar function suggest that motor learning occurs by adjustments of the strength of parallel fiber synapses onto Purkinje neurons, based on the relative timing of the parallel fiber activity and 'error signals' conveyed by the climbing fibers arising from the inferior olive. It is now well established that coincident activation of parallel and climbing fibers induces LTD at the parallel fiber–Purkinje cell synapse (Bear & Linden 2001; Ito 1989). Climbing fiber activation is permissive for LTD by elevating intracellular calcium ion concentration; however, the signal that marks the parallel fiber synapse for depression is local activation of Gp1 mGluRs. In the case of cerebellar LTD, the critical receptor is mGluR1 rather than mGluR5. However, similar to the situation in the hippocampus, mGluR-dependent LTD in the cerebellum requires activation of ERK (Endo & Launey 2003) and the translation of pre-existing mRNA (Karachot *et al*. 2001) and is expressed as a loss of AMPA receptors (Steinberg *et al*. 2004). Very recently, cerebellar LTD was examined in the *Fmr1* KO mouse and found to be increased, consistent with the predictions of the mGluR theory (B. Oostra, personal communication). This change in cerebellar synaptic plasticity correlated with impairments in motor learning as assessed by associative eyeblink conditioning. Moreover, comparable defects in eyeblink conditioning were observed in humans with fragile X syndrome. These results suggest that dampening signaling through mGluR1 also could be beneficial in treating fragile X syndrome. However, the therapeutic window for mGluR1 antagonists may prove to be too narrow, because mGluR1 is essential for normal cerebellar function.

Group 1 metabotropic glutamate receptors also play a central role in synaptic plasticity in the striatum believed to be important for the development of habitual motor routines (Gerdeman *et al*. 2003; Gubellini *et al*. 2004). High-frequency stimulation of the cortical afferents to striatal medium spiny neurons can elicit either LTP or LTD, depending on a number of variables such as age and position within the striatum. Both the forms of synaptic plasticity require activation of mGluR1 and/or mGluR5; LTP requires, in addition, activation of NMDA receptors. At present, the picture is most clear for LTD in the dorsal-lateral striatum. Similar to the parallel fiber–Purkinje cell synapse, LTD is induced at corticostriatal synapses by the simultaneous activation of Gp1 mGluRs and a rise in postsynaptic calcium entering through voltage-gated channels. However, unlike the cerebellum, induction of striatal LTD also requires dopamine signaling, and LTD is expressed presynaptically as a reduced probability of glutamate release. The retrograde messenger, signalling from postsynaptic mGluRs to the presynaptic axon terminal, is an endocannabinoid acting on presynaptic CB1 receptors (Gerdeman *et al*. 2002). A role for translation of pre-existing mRNA following mGluR activation has not yet been examined, although this is a clear prediction of the mGluR theory.

The theory also predicts excessive Gp1 mGluR-dependent LTD will be observed in the striatum of the *Fmr1* KO mice. It has been suggested that the development of stereotypies is a consequence of LTD-like changes in the dorsolateral striatum (Graybiel *et al*. 2000). Indeed, striatal activation is deficient in humans with obsessive-compulsive disorder (Graybiel & Rauch 2000; Rauch *et al*. 1997), consistent with the possibility of excessive LTD. Antagonists of Gp1 mGluRs (mGluR5, in particular) could be beneficial for the treatment of compulsive motor routines in fragile X.

Other symptoms and suspicious coincidences

Other symptoms associated with fragile X include obesity, irritable bowel and hyperalgesia. The neurobiological basis for these symptoms remains to be determined in fragile X. Remarkably, however, there is evidence that all of them could be potentially treated with mGluR5 antagonists.

Obesity is likely to arise from altered signaling in the hypothalamus. The ventromedial hypothalamus responds to hormones that signal energy demand and incites feeding behavior via connections with the lateral hypothalamus (Saper *et al*. 2002). Both the ventromedial and the lateral hypothalamus have high levels of mGluR5 expression (van den Pol *et al*. 1995). Very recently, it was reported that mGluR5 KO mice have diminished appetite and weigh less than wild-type littermates. Moreover, treatment of rats with an mGluR5-selective antagonist decreased food intake and caused weight loss (Bradbury *et al*. 2004). These findings suggest that exaggerated mGluR5 signaling could also be responsible for obesity in fragile X.

Gut motility is controlled by a complex interaction of the enteric and central nervous systems (Hunt & Tougas 2002). A population of secretomotor neurons in the ileum contain mGluR5 (Liu & Kirchgessner 2000). Local application of mGluR5 agonists and antagonists increase and decrease, respectively, gut motility (Hu *et al*. 1999).

It is interesting that a majority of patients with irritable bowel syndrome also have altered pain perception (Hunt & Tougas 2002), and hyperalgesia is a common complaint in fragile X. Metabotropic glutamate receptor 5 is expressed by nociceptive C fibers, where it has been implicated in the mechanisms of hyperalgesia.

Concluding remarks

Obviously, there is far more to fragile X than mGluRs. However, evidence continues to accrue that one consistent consequence of the loss of FMRP in neurons is exaggerated signaling via Gp1 mGluRs. This single defect could account for highly diverse neurological and psychiatric symptoms in fragile X syndrome. An exciting prospect is that some or all of these symptoms could be improved by drug therapies that specifically target signaling by Gp1 mGluRs.

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