

## ORIGINS OF EPILEPSY IN FRAGILE X SYNDROME

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*Fragile X syndrome is the leading heritable form of cognitive impairment and the leading known monogenic disorder associated with autism. Roughly one-quarter of children with this disorder have seizures, most of which are relatively benign and are resolved beyond childhood. Because of the prevalence of fragile X syndrome, numerous animal models have been developed and electrophysiological studies have taken place to investigate its pathogenesis. The investigations have yielded a wealth of information regarding the synaptic dysfunction that underlies the hyperexcitability and epileptiform features associated with this disorder.*

Fragile X syndrome is the most common heritable form of cognitive impairment and the principal single-gene disorder associated with autism currently known (1,2). The disorder arises when a CGG-repeat tract in the 5' noncoding region of the fragile X mental retardation 1 (*FMR1*) gene exceeds approximately 200 repeats (i.e., the full mutation range), at which point the gene becomes hypermethylated and transcriptionally silent (3). The absence of the *FMR1* protein, FMRP, is responsible for the syndrome's clinical phenotype (4–7). The frequency of full mutation alleles in the general population is approximately 1 in 2,500 (8,9). Physical features of fragile X syndrome typically include prominent ears, long face, high-arched palate, macroorchidism, and hyperextensibility of finger joints. Approximately 85% of males and 25% of females experience cognitive impairment (IQ < 70); however, nearly all patients present with behavioral dysregulation, with males tending to present with attention deficit hyperactivity disorder and

aggression, while females are more prone to shyness and social withdrawal (8,10).

FMRP is an RNA-binding protein that is believed to have multiple functions, including involvement in the dendritic transport of various mRNA species (11) and the translational regulation of mRNAs whose protein products are involved in synaptic development, function, and plasticity (12). Among known targets of FMRP-coupled translational downregulation are: 1) the microtubule-associated protein 1B (MAP1B), which is important for modulating microtubule-coupled growth of dendritic spines and for dendritic arborization (13,14), and 2) Arc, which plays a role in the internalization of subunits of AMPA (15,16) and GABA<sub>A</sub> (17) receptors.

One important characteristic of fragile X syndrome is the cooccurrence of seizures in 10 to 20 percent of individuals with full mutations (18,19). Seizure patterns on EEG typically reflect features of benign focal epilepsy of childhood (especially benign childhood epilepsy with centrotemporal spikes, also known as benign Rolandic epilepsy). In the study by Berry-Kravis involving 16 children with fragile X syndrome and epilepsy, 12 children exhibited partial seizures, with 10 of the 12 having an EEG with centrotemporal spikes (19). In addition, 23% of the children who did not have seizures displayed abnormal patterns on EEG, typically centrotemporal spikes. For most individuals, seizures are readily controlled and tend to disappear in adolescence. Therefore, there are similarities between epilepsy in individuals with Rolandic epilepsy and fragile X syndrome, and any mechanism postulated to explain epileptogenesis in fragile X syndrome must account for the relatively benign seizure manifestations. This review will next consider mechanisms of neuronal dysfunction in fragile X syndrome that might underlie hyperexcitability leading to seizures in this disorder.

### The Metabotropic Glutamate Receptor Theory for Fragile X Syndrome

A key advance in the understanding of the molecular basis of fragile X syndrome came with the observation in 2002 by Huber et al. that mice lacking FMRP displayed enhanced long-term depression in hippocampal neurons (20) and that this depression was dependent on protein synthesis (21,22). Further, the investigators determined that the process could be inhibited by blocking the metabotropic glutamate receptor 5 (mGluR5) with agents such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP) (23). In this model, FMRP normally functions to downregulate the translation of proteins that are involved with the internalization of the ionotropic AMPA glutamate receptor from the postsynaptic surface. Thus, in the absence of postsynaptic

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FMRP, stimulation of mGluR5, either by receptor agonists or glutamate release from the presynaptic terminus, results in increased postsynaptic protein translation, leading in turn to excess internalization of AMPA receptors and eventual weakening of the synaptic connection.

Over the past several years, a great deal of evidence has accumulated to support the model elaborated by Huber and colleagues, which is termed the “mGluR theory of fragile X mental retardation” (24). The mGluR model is capable of explaining a number of the physical and behavioral features of fragile X syndrome and has been predictive for correction of several aspects of the phenotype in various animal models (25,26), including improved seizure activity in a *Fmr1* knockout mouse model with audiogenic seizures (27–29). One consequence of the enhanced protein synthesis in the absence of postsynaptic Fmrp (i.e., in the knockout mouse) is increased internalization of AMPA receptors on the postsynaptic surface. Interestingly, the augmented AMPA receptor internalization (a facet of the increased long-term depression observed in the knockout mouse) no longer requires protein synthesis, suggesting that the elevated protein levels present in the postsynaptic compartment are sufficient to establish the enhanced long-term depression (30).

One potential caveat concerns the agents used in many of the animal studies, particularly those involving mGluR5 inhibitors (e.g., MPEP) or AMPA-receptor agonists, is that the drugs may have off-target effects that mimic the target effect. To resolve this uncertainty, Dölen and coworkers crossed *Fmr1* knockout mice with animals that were heterozygous for deletion of the *Grm5* gene (50% reduction in mGluR5), thus mimicking drug-induced reductions in mGluR5 activity (16). The resulting mice, *Fmr1(-/Y)Grm5(+/-)*, displayed substantial correction of defects in experience and conditioning (i.e., ocular dominance plasticity and inhibitory avoidance extinction), normalization of dendritic spine density, a return to normal basal protein synthesis, attenuated susceptibility to audiogenic seizures, and rescue from early accelerated growth. These results clearly established that the enhanced response to stimulation of the mGluR5 receptor plays a critical role in many of the phenotypic characteristics of fragile X syndrome. Finally, Qiu et al. observed that kindling promoted prolonged seizure activity and severe mossy fiber sprouting in the *Fmr1* knockout mouse and that this behavior could be at least partially blocked using either NMDA-receptor or mGluR5 inhibitors (31).

### Epileptogenic Mechanisms in Fragile X Syndrome

The mGluR model is capable of explaining many of the phenotypic features of fragile X syndrome, and thus, providing a basis for the development of targeted interventions for this disorder. Yet, altered postsynaptic function arising from the absence of FMRP does not readily explain the CNS hyperexcitability and

EEG epileptiform features associated with this disorder. However, several recent studies have begun to reveal the connection.

In a recent investigation on group I mGluR-mediated epileptogenesis, Bianchi et al. provided compelling evidence that a voltage-gated inward current,  $I_{mGluR(V)}$ , is the cellular basis for the epileptogenic behavior induced by activation of the mGluR5 receptor (28,32–34). Specifically, Bianchi et al. demonstrated that stimulation of mGluR5, by the agonist dihydroxyphenylglycine in mouse hippocampal slices, led to prolonged epileptiform discharges that lasted more than 1 hour after washout of the agonist. Moreover, this inward current could be suppressed by inhibitors of downstream signaling pathways that mediate group I mGluR-coupled translation (e.g., tyrosine kinase, extracellular signal-regulated kinase [ERK]1/2) (35,36). Remarkably, glutamate stimulation of glutamergic synapses did not recapitulate this effect in wild-type mice, whereas  $I_{mGluR(V)}$  was activated in hippocampal preparations from *Fmr1* knockout mice. The authors conclude that the induction of  $I_{mGluR(V)}$ , “as a form of synaptic plasticity mechanism underlying epileptogenesis,” is a global neuronal action rather than a synapse-specific event. Thus, activation of mGluR5 in multiple synapses in the absence of FMRP translational control leads to a form of neuronal plasticity that involves heightened electrical excitability. The carrier of  $I_{mGluR(V)}$  is not known with certainty; however, evidence supports one or more of the transient receptor potential canonical channels (37).

Evidence for a connection between the absence of *Fmr1* and epileptogenesis in the knockout mice was extended in the study of neocortical circuits by Gibson et al. (38). In agreement with the observations of Bianchi et al., the authors observed increased intrinsic excitability in excitatory neurons from the knockout. However, there appeared to be an imbalance between this excitability and a relatively decreased excitatory drive present at fast-spike inhibitory neurons. The net result was a prolonged neocortical circuit activity (termed, UP state), induced by thalamic input. The heightened circuit activity, coupled with a less synchronous network inhibition, is proposed as the underlying mechanism that leads to the EEG abnormalities and epilepsy associated with fragile X syndrome. Thus, the failure to properly modulate the mGluR5 response in the absence of FMRP results in neuronal hyperexcitability, mediated in part by the generation of a voltage-gated inward current, which in turn alters (i.e., reduces) excitatory input to inhibitory neurons and results in a net increased excitability of neuronal circuits (39).

### The Role of GABA Receptors

There is now abundant evidence that the increased excitability of mouse hippocampal and neocortical circuitry occurring with fragile X syndrome is due to dysregulation of glutamergic neurons and that this altered function can disrupt the

normal actions of inhibitory GABAergic neurons. Solid evidence also exists to show that downregulation of GABA receptor subunits occurs both at the mRNA and protein level—a situation that would further increase the excitatory character of limbic and cortical circuits, or both (40–42). Recently, D’Hulst et al. demonstrated that in addition to reductions in GABA<sub>A</sub> subunits, there is also altered expression of a number of enzymes involved in the metabolism of GABA (17). The investigators observed similar forms of GABA dysregulation in both mouse and *Drosophila* models of fragile X syndrome. In aggregate, these results point to a deficiency in the function of the GABAergic system in the *Fmr1* knockout mouse that would further upset the balance between excitatory and inhibitory functions within the CNS, all in the direction of increased excitatory behavior.

On a structural level, Selby et al. studied the architecture of GABA-releasing neurons in the somatosensory cortex of the *Fmr1* knockout mouse and found evidence for a reorganization of inhibitory circuits that was accompanied by a reduction in the densities of GABA-releasing interneurons (43). A separate investigation of function of GABAergic neurons within the subiculum revealed that tonic, but not phasic, GABA<sub>A</sub> currents were downregulated in the *Fmr1* knockout mouse relative to wild-type controls (44). These results were associated with reductions in tonic GABA<sub>A</sub> receptor subunits.

### Clinical Correlations and Prospects for Therapeutic Intervention

The remarkable growth in knowledge of the pathogenesis of fragile X syndrome and specifically, regarding the linkage between abnormal neural function and epileptogenesis, presents numerous possibilities for targeted interventions (4). Perhaps the most advanced avenue for targeted treatment could be based on blocking the activity of the mGluR5 receptor itself, thus compensating for the absence of downstream control by FMRP. At present, a number of clinical trials are underway with various mGluR5 inhibitors. A recently completed open-label, single-dose pilot trial ( $n = 12$ ) of the mGluR5 agonist, fenobam, demonstrated no significant adverse effects and a trend toward improvement, as measured by improved prepulse inhibition (at least a 20% improvement over baseline in 6 of 12 individuals) (45). A second open-label treatment trial ( $n = 15$ ) tested the effects of lithium, which reduces mGluR5 activation of downstream processes (46). There was significant improvement in several behavioral and learning measures, along with enhanced ERK activation, indicating the need for larger clinical trials.

Studies of dysregulation of GABA function suggest that the GABA<sub>A</sub> receptor is also a potential therapeutic target (47). In this regard, Chang et al. discovered that the *Fmr1* mutant *Drosophila* die during development if fed a high glutamate diet, consistent with the mGluR model for excess activation (48).

The authors exploited this lethal phenotype to screen for small molecules that would rescue the flies and found several, including GABA, that rescued the phenotype, thus providing additional evidence that GABA-receptor agonists may have a beneficial therapeutic effect. Finally, there is substantial evidence that GABA-receptor agonists, such as the neurosteroid allopregnanolone and a related analog, ganaxolone, possess significant antiseizure activity (49,50). It would be valuable to have these agents subjected to clinical trials for fragile X syndrome and, in particular, for the associated seizures.

In summary, epilepsy associated with fragile X syndrome represents an opportunity to explore mechanisms of hyperexcitability in a disorder for which the molecular pathophysiology is unique and specific (51). Seizures occurring in conjunction with fragile X syndrome are generally mild, tend to disappear in childhood, typically respond to anticonvulsant treatment, and are associated with an EEG pattern of centrottemporal spikes. In several respects, the clinical and electrographic aspects of seizures in fragile X syndrome resemble those of the benign focal epilepsies of childhood. Whether these similarities are coincidental or mechanistically related remains an intriguing question for future investigation. The type of (and even need for) antiepileptic therapy for individuals with fragile X seizures must be weighed against potential adverse effects, which could be unique with this syndrome. Ideally, pathophysiological insights as reviewed here will lead to therapeutic interventions targeted to the specific molecular defects in fragile X syndrome.

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