Keywords: autism, FMRP, fmr1, Fragile X, GABA, mental retardation, mGluR5

Fragile X syndrome (FXS), the most common single gene cause of mental retardation, is securely associated with mutations in the fragile X mental retardation 1 gene, FMR1 (Fu et al. 1991; Verkerk et al. 1991; Feng et al. 1997; Musumeci et al. 1999; Hagerman et al. 2009). Nevertheless, identification of consequences of loss of the protein product of FMR1, the fragile X mental retardation protein FMRP, has proven difficult. In this issue of Cerebral Cortex, 2 papers, one by Curia et al. and the other by Qiu et al., demonstrate that FMRP normally navigates the treacherous road of hippocampal excitation and inhibition, controlling the γ-aminobutyric acidergic (GABAergic) brakes and glutamatergic accelerator. Without FMRP in the driver’s seat, the journey becomes perilous, resulting in excess excitation and enhanced seizure vulnerability.

FMRP, an RNA-binding protein, potentially regulates thousands of genes (Ashley et al. 1993; Brown et al. 2001). Thus, determining molecular mechanisms for diverse FXS phenotypes remains challenging. FMRP not only regulates translation in the cell body (Khandjian et al. 1996); it is also transported to dendrites to influence local RNA processing. Other proposed FMRP functions include mRNA transport, including GABA_A subunit mRNA and mRNA stability (Zalfa et al. 2007). Consequences of FMRP loss of function may extend beyond translation regulation: It can also function in the RNA induced silencing complex (RISC) nuclease complex influencing translation of mRNAs through regulation of small interfering RNAs (Caudy et al. 2002; Ishizuka et al. 2002). This molecular complexity suggests that functional assessment of local circuits and synaptic activity in animal models of FXS—rather than gene-by-gene analysis—may refine hypotheses of molecular targets of FMRP loss of function and their contribution to brain dysfunction.

One emerging hypothesis is that FMRP regulates the balance of excitation and inhibition in neural circuits, particularly in the hippocampus. Altered GABA_A efficacy has long been thought to contribute to FXS symptoms (D’Hulst and Kooy 2007), particularly the high frequency of seizures in FXS patients. There is also general evidence that metabotropic glutamate receptors contribute to seizure susceptibility, perhaps including that in FXS. The anticonvulsant antagonist 2-methyl-6-phenylethynyl-pyridine (MPEP), which targets mGluR5, raises seizure threshold in normal mice (Chapman et al. 2000). The fmr1 knockout mouse, a model for FXS (Bakker et al. 1994), is more susceptible to audiogenic seizures, further supporting altered balance of inhibitory and excitatory circuits (Musumeci et al. 2000). FXS may also disrupt information encoding and storage. FMRP is implicated long-term depression (LTD) through mGluR5, and in fmr1 knockout mice, mGluR-LTD is enhanced (Huber et al. 2002; Bear et al. 2004). Clearly, hippocampal synaptic mechanisms and circuits implicated in seizures as well as normal information storage may be targets in FXS.

In this issue of Cerebral Cortex, Curia et al. focus on consequences of FMRP loss of function for inhibitory mechanisms in the hippocampal subiculum, which receives primary input from CA1 pyramidal cells and reflects the output of hippocampal processing. They found a shift in holding current in wild type (WT) but not fmr1 knockouts in response to treatment with a noncompetitive GABA_A antagonist, picrotxin. In addition, expression of both the GABA_A δ and γ subunit is diminished. Previous studies have shown that GABA_A receptor δ subunit mRNA and protein levels are substantially reduced throughout the fmr1 knockout forebrain (El Idrissi et al. 2005; D’Hulst et al. 2006; Gantois et al. 2006); however, changes in of the GABA_A γ subunit are regionally restricted (Gantois et al. 2006), possibly excluding the neocortex. Thus, Curia et al. support previous work showing impaired GABA_A receptor function in FXS and extend it by anchoring altered inhibitory transmission and gene expression to specific circuits in distinct forebrain regions. Such circuit-specific changes may ultimately underlie discrete behavioral deficits in FXS.

The second FXS-related paper in this issue of Cerebral Cortex used an established epilepsy model—amygdala kindling, which relies on repetitive subthreshold electrical stimulation to increase seizure susceptibility (Godard et al. 1969; Racine 1972)—to explore the role of FMRP in seizures. Fully kindled WT mice given a single seizure-inducing stimulus displayed greatly increased fmr1 mRNA and FMRP compared with fully kindled WT mice without the seizure-inducing stimulus. fmr1 knockout mice displayed accelerated kindling with lower threshold, more severe seizures, and prolonged after-discharges. FMRP may normally suppress seizures by regulating metabotropic glutamate receptor activity. The mGluR5 antagonist MPEP had no effect on kindling development in WT mice (potentially due to FMRP-dependent regulation); however, it decelerated kindling in fmr1 knockouts. FMRP may not directly regulate mGluR5 translation; instead, local changes in hippocampal circuits may impact mGluR5-mediated synaptic transmission. Among possible targets, Qiu et al. report increased granule cell mossy fiber sprouting in fully kindled fmr1 knockouts. Thus, FMRP loss of function compromises specific local circuits in parallel with altered synaptic activity. Such local changes may contribute to increased seizure susceptibility as well as behavioral consequences in FXS.

The work of Curia et al. and Qiu et al. adds to the small body of literature showing that altered forebrain circuit function—
Figure 1. Summary of the major findings presented by Curia et al. and Qiu et al. in this issue of Cerebral Cortex. Data from these two papers place FMRP, the protein product of the FMR1 gene mutated in FXS in the driver’s seat, controlling the “brakes” and “gas” of inhibition and excitation in hippocampal and parahippocampal circuits. Together, the papers show that fmr1 knockout (KO) mice, an animal model for FXS, have decreased inhibition (the brakes) but increased excitability (the “accelerator” or the “gas”) compared with wild type (WT) mice. Neuronal excitability braking mechanisms (red arrows) are generally decreased in fmr1 knockout mice primarily by decreased GABA effectiveness, whereas increased excitability (green arrows) occurs due to modulation of signaling via the metabotropic glutamate receptor, mGluR5. Curia et al., and Qiu et al. suggest that these changes may be limited to hippocampal and parahippocampal cortices, perhaps suggesting a local pathogenic mechanism for increased seizure susceptibility in FXS.

particularly imbalance of inhibition and excitation—is an essential consequence of loss of FMRP function. Single gene mutation diseases with diverse phenotypes often pose the difficult question of how loss of function of relatively ubiquitous expressed genes produce distinct, localized phenotypes. FMRP, expressed throughout the brain, disproportionately affects cortical circuits even though hundreds to thousands of genes are potentially modulated by FMRP. These new studies reinforce the centrality of hippocampal and parahippocampal cortical circuits in FXS phenotypes, as well as potential therapeutic value of drugs that modulate GABAergic or mGluR5 function (Berry-Kravis et al. 2009). It remains to be seen whether robust fmr1 circuit phenotypes in mice are also seen in human FXS, particularly for mental retardation and other cognitive changes. Nevertheless, Curia et al. and Qiu et al. securely place FMRP in the driver’s seat, controlling the “brakes” and accelerator to provide a smooth ride with appropriate inhibition and excitation in normal forebrain circuits and an uncertain journey when it is not at the wheel, as in FXS (see Fig. 1).

Funding
National Institutes of Health (MH073155 to J.E.B.).

Notes
Thanks to Dr A. LaMantia for numerous comments and suggestions. Conflict of Interest: None declared.

Address correspondence to Dr Jay E. Brenman. Email: brenman@med.unc.edu.

References


