Advances in understanding fragile X syndrome and related disorders

Liesbeth Rooms and R. Frank Kooy

Department of Medical Genetics, University of Antwerp, Antwerp, Belgium

Correspondence to Dr R.F. Kooy, Department of Medical Genetics, University of Antwerp, Universiteitsplein 1, 2610 Antwerp, Belgium
Tel: +32 3 275 9760; fax: +32 3 275 9722;
e-mail: frank.kooy@ua.ac.be

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Purpose of review

Fragile X syndrome is the most common form of inherited intellectual disability. Over the past 2 decades, insights into the cause of this disease have increased tremendously. This review will highlight recent discoveries with an emphasis on biochemical pathways affected in the disorder that are potentially amenable to treatment.

Recent findings

Recent work in the field demonstrated that multiple pathways are deregulated as a consequence of the *FMR1* gene inactivation in patients with fragile X syndrome. In fragile X patients, no fragile X mental retardation protein is formed and thereby protein translation is compromised. As a consequence, a variety of biological pathways are disturbed. These pathways include mainly the metabotropic glutamate receptor and gamma-aminobutyric acid (GABA)ergic pathways, but recently potassium channels and the muscarinic cholinergic receptor have also been implied in fragile X syndrome. An overview is given of the potential therapeutic targets and clinical studies that have been performed.

Summary

The gene defect underlying fragile X syndrome was discovered back in 1991. Since then, there has been enormous progress in our understanding of the molecular basis of the disease. Excitingly, our insights have now reached a next phase in which therapy specifically targeting the underlying molecular defect becomes feasible.

Keywords

FMR1, fragile X syndrome, fragile X-associated tremor/ataxia syndrome, therapy

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Introduction

The *FMR1* gene coding for fragile X mental retardation protein (FMRP) can elicit three distinct syndromes: fragile X syndrome (FXS), fragile X-associated tremor/ataxia syndrome (FXTAS) and premature ovarian insufficiency (POI). FXS is the leading cause of inherited intellectual disability, affecting approximately one in 2500 to one in 6000 [1]. This disorder is caused by the elongation of a CGG repeat above 200 units in the 5′ untranslated region of *FMR1*, leading to a hypermethylation of the promoter region followed by transcriptional inactivation of the gene. Apart from the intellectual impairment, patients present with typical facial characteristics such as an elongated face with prominent forehead, a protruding jaw, large ears and macroorchidism. In addition, patients may show behavioural problems including autistic-like behaviour, sleeping problems, anxiety, mood disorders and aggression. Another prominent feature of the disorder is neuronal hyperexcitability, manifested by hyperactivity, increased sensitivity to sensory stimuli and a high incidence of epileptic seizures [2].

CGG repeat expansions in size in between the normal range of 5–54 repeats and the full mutation range are called premutations. Although carriers of premutations do not suffer from FXS, they do display a range of clinical features. FXTAS is an adult onset neurodegenerative disorder among many older adult carriers of premutation expansions. Features of this disorder include slowly progressive gait ataxia, intention tremor, dementia, Parkinsonism and neuropsychiatric symptoms [3]. POI, defined as cessation of menses prior to age 40, is seen in about 20% of female premutation carriers [4].

The *FMR1* gene was discovered in 1991 and has been shown to be involved in numerous biochemical processes and pathways (Table 1). The gene product, FMRP, is expressed in most cell types, including neurons. FMRP contains five different functional motifs: two different RNA-binding domains, a nuclear localization signal, a nuclear export signal and two coiled coils involved in protein–protein interaction. It is an RNA-binding protein known to regulate mRNA trafficking, mRNA stability and the translation of a number of neuronal transcripts.

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Although FMRP is estimated to interact with approximately 4% of total brain mRNAs, only a small subset of those have been validated experimentally [5]. Clinical manifestations in FXS are believed to result from a defective synapse function, as FMRP affects local protein synthesis and plasticity in the dendritic spines. Interestingly, over the last years, the increased insights into the pathophysiology have led to drug trials in animal models and patients. This review will highlight recent discoveries with an emphasis on affected pathways that are amenable to treatment.

Key points

- Research in fragile X syndrome, the leading cause of inherited intellectual disability, has reached a next phase in which therapy targeting the underlying molecular defect rather than merely treating the symptoms becomes feasible.
- The metabotropic glutamate receptor signal transduction cascade and the gamma-aminobutyric acid (GABA)ergic pathway are promising targets for targeted therapy.
- Additional drug trials were initiated with minocycline targeting matrix metalloproteinase 9 and lithium inhibiting glycogen synthase kinase (GSK)3, encouraging further studies in fragile X patients.
- *FMR1* premutation carriers, for a long period regarded as symptomless, can develop fragile X-associated tremor/ataxia syndrome and fragile X-associated primary ovarian insufficiency.

Toward targeted therapy in fragile X syndrome: glutamatergic and GABAergic pathways

A primary pathway involved in FXS is the metabotropic glutamate receptor (mGluR) signal transduction cascade [6•,7]. In brief, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor internalization triggered by group I mGluR stimulation is exaggerated in FXS as a consequence of absence of the translational inhibitor FMRP [8]. In its turn, a reduced number of AMPA receptors in the synaptic cleft results in enhanced mGluR dependent long-term depression (LTD), a process believed to be involved in memory and learning. This observation predicted that dampening the mGluR signalling would improve the clinical symptoms of FXS patients. This theory was experimentally validated by the analysis of genetically modified rescue mice [9] and by treatment with drugs like 2-methyl-6-(phenylethynyl)-pyridine (MPEP), which was capable of rescuing audiogenic seizures, AMPA receptor internalization, marble burying and spine morphology in animal models [10,11•]. Levenga *et al.* [12••] used AFQ056, a novel and more specific mGluR5 inhibitor than MPEP, as a putative potent therapeutic. This drug rescued the spine length and prepulse inhibition phenotype of fragile X mice. Encouraged by the results in animal models, Novartis (Basel, Switzerland) conducted a phase II fragile X trial using AFQ056. Initially, no effect on the behaviour was observed when the complete set of 30 patients was compared with the controls [13•]. However, when they looked at the epigenetic modification of the *FMR1* gene, it appeared that only a subgroup of seven patients had a fully methylated promoter and, thus, complete absence of *FMR1* mRNA. The promoter region in the other patients appeared partially methylated, presumably resulting in residual gene expression. When the performance of the fully methylated patients was compared with the controls, a significant improvement on stereotypic behaviour, hyperactivity and inappropriate speech was observed. If these results can be validated in subsequent studies, this may suggest that AFQ056 is suitable to treat patients with a full *FMR1* mutation. In concordance with these results, Seaside Therapeutics (Cambridge, Massachusetts, USA) presented significant improvement in sociability and communication in fragile X patients in a phase II clinical trial with the selective receptor $GABA_B$ receptor agonist STX209, better known as arbaclofen, on the 12th NFXF International Fragile X Conference in Dearborn

Table 1 Disorders caused by mutations in the *FMR1* gene

Disorder	Number of CGG repeats	Methylation of repeat	FMR1 mRNA	FMR1 protein	Primary clinical symptoms	Pathways and systems affected that are (potentially) amenable to treatment
Fragile X syndrome	>200	Yes	Absent	Absent	Intellectual disability	mGluR pathway, GABAergic system, GSK3
					Dysmorphism	MMP9, PI3K, potassium channels, mAChR
					Behavioural abnormalities	
FXTAS	50–200	No	Elevated	Normal or slightly reduced	Neurodegeneration	HDAC
					Intranuclear inclusions in brain	
POI	50–200	No	Unknown	Unknown	Premature cessation of menses	

FXTAS, fragile X-associated tremor/ataxia syndrome; GABA, gamma-aminobutyric acid; GSK, glycogen synthase kinase; HDAC, histone deacetylases; mAChR, muscarinic cholinergic receptors; mGluR, metabotropic glutamate receptor; PI3K, phosphoinositide 3-kinase; POI, premature ovarian insufficiency.

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(Michigan) in July 2010. $GABA_B$ receptors are found presynaptically on glutamatergic synapses and modulate the release of glutamate. Stimulation of this receptor, therefore, diminishes the excessive glutamate signalling in FXS [14]. A phase III trial will be initiated in the course of 2011.

Previously, our group demonstrated the involvement of the GABAergic system in FXS and argued that the $GABA_A$ receptor might be a novel target for treatment [15]. $GABA_A$ receptors are the main inhibitory receptors in brain involved in anxiety, epilepsy, depression, sleep problems, learning and memory; all processes disturbed in FXS. We initially observed decreased expression at the mRNA level [16]. Since this description, several other groups have confirmed abnormalities in the GABAergic system in the fragile X aetiology, including decreased protein levels of $GABA_A$ receptor subunits in adult mice [17,18]. Moreover, a study was performed in the forebrain of fragile X mice at postnatal days 5 and 12, showing differential expression of several components of the GABAergic system at different developmental stages [18]. These changes in expression may have significant implications, as the GABAergic system switches from excitatory to inhibitory during this developmental period. Other groups confirmed the involvement of the GABAergic system using electrophysiological recordings [19–21]. Moreover, Olmos-Serrano *et al.* [22••] observed dampened inhibitory neurotransmission, reduction in inhibitory synapse number and decreased cellular and synaptic levels of GABA in the amygdala of fragile X mice.

The advantage of targeting the GABAergic system is that numerous drugs of clinical relevance binding to this receptor are available [23]. An indication that these will be effective comes from work on d*Fmr1*-deficient flies that die when reared on food containing increased levels of glutamate [24]. This lethality was rescued by the addition of GABA itself, a GABA reuptake inhibitor and creatinine, a potential activator of the $GABA_A$ receptor. The most widely used GABAergic drugs are the benzodiazepines, but they show unwanted side-effects such as tolerance, dependence and sedation. Fortunately, more selective GABAergic drugs with few side-effects are available for testing, such as TPA-023. Another type of promising drugs are the neurosteroids, potent allosteric modulators of the $GABA_A$ receptor, including ganaxolone, which is now being tested in phase II clinical trials for the treatment of specific seizure disorders [25]. We were able to rescue the audiogenic seizure phenotype in fragile X mice by treatment with ganaxolone (Heulens *et al.*, in preparation).

The GABAergic and mGluR theories might be mechanistically related. Recently, our group hypothesized that the $GABA_B$ receptor may serve as the functional link between both theories, as this metabotropic receptor regulates glutamate release at glutamatergic synapses [26]. In fragile X patients, a reduced spill over of GABA from the GABAergic synapses to the presynaptic $GABA_B$ receptors may induce a reduced inhibition of neurotransmitter release in the latter and so induce mGluR signalling.

Other promising drug targets

Several other drug trials have been set up and are in the planning. Detailed overviews of all ongoing and planned trials were recently presented [27,28]. In one of the first targeted treatment trials in fragile X patients, minocycline was used [29]. Matrix metalloproteinase 9 (MMP9) is elevated in hippocampus of fragile X mice [30]. Treatment with minocycline, a tetracycline derivative that inhibits MMP9, rescued the spine protrusion phenotype in *Fmr1*-knockout hippocampal neurons and improved performance in behavioural tests. In the *Drosophila* FXS model, minocycline treatment prevented structural over elaboration and synaptic developmental defects in a wide range of neural circuits [31]. Overexpression of tissue inhibitor of matrix metalloproteinase, a tissue inhibitor of MMP, confirmed that MMP inhibition was responsible for the alleviatory effects of minocycline. Encouraged by these results, a pilot study in 20 fragile X patients was performed and significant improvements across a range of behaviours were seen without serious side-effects [29]. However, a placebo-controlled trial is needed, especially as minocycline-induced autoimmunity could occur in patients.

Lowered inhibitory serine phosphorylation of brain glycogen synthase kinase (GSK)3 is believed to be a consequence of increased mGluR signalling in fragile X mice. Lithium directly inhibits GSK3. A series of studies shows that treatment with this drug, which is already approved for use in patients with bipolar disorder, ameliorated the behavioural deficits in both fragile X mice and patients [32,33,34•,35]. These findings encourage further clinical trials in fragile X patients with this drug.

Novel pathways of potential therapeutic relevance

Recently, additional signal transduction pathways have been reported to be deregulated in the absence of FMRP [36,37]. FMRP was reported to control mRNA translation, synaptic localization and enzymatic activity of the catalytic subunit p110β of phosphoinositide 3-kinase (PI3K), a downstream signalling molecule of many cell surface receptors [38,39•]. As a consequence of FMRP

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deficiency, basal PI3K activity at the synapses is increased. This excessive PI3K activity might underlie the exaggerated mGluR-mediated protein synthesis observed in FXS. PI3K antagonists can rescue the excessive dendritic spine density and the increased internalization of AMPA receptors, suggesting PI3K as a novel therapeutic target. PI3K is an upstream regulator of mammalian target of rapamycin (mTOR). Enhanced mTOR signalling in the hippocampus of fragile X mice may serve as a functional link between the overactivation of group I mGluRs and aberrant synaptic plasticity at CA1 synapses in the fragile X mouse. Components of this signalling cascade may also become attractive targets for therapy.

The majority of reports indicated that FMRP is a translational inhibitor [40,41]. Recent findings, however, suggested that FMRP might diversely regulate neuronal potassium conductance. Gross *et al.* [42] showed that FMRP positively regulates Kv4.2 mRNA in hippocampus and cortex, whereas other studies uncovered the negative regulation of Kv3.1b by FMRP [43]. In addition, FMRP alters gating properties of the Slack potassium channel via direct protein interactions [44••]. Potassium channel modulators are, therefore, attractive novel targets for rational therapy.

Muscarinic cholinergic receptors, G protein-coupled receptors mediating the actions of acetylcholine, have also been implied as the cause of fragile X [20]. Activation of muscarinic M1 receptors by carbachol resulted in enhanced LTD in the fragile X mouse [36]. Addition of a selective muscarinic M1 antagonist, dicyclomine, was used to evaluate the effects of decreasing M1 receptor activity in the fragile X mouse. A modulation of perseverative behaviour and audiogenic seizures without sedative effects was observed [45]. Although this study suggests muscarinic antagonists as a novel drug target, it should be realized that M1 receptors are also involved in learning and memory, and adverse effects on cognition might become an unwanted side-effect of treatment.

Phenotypic consequences of premutation alleles

Premutation alleles are quite common in the general population, with a frequency of 1:250 males and 1:130 females [46]. Although carriers of a premutation have long been regarded as symptomless, recent studies challenge this assumption. Forty percent of male carriers and 8% of female carriers will develop FXTAS, with the severity of the symptoms correlating with the number of CGG repeats [47,48]. The neuropathological hallmark of FXTAS is an intranuclear inclusion present in both neurons and astrocytes of the central nervous system, with the number of these inclusions being significantly associated with the number of CGG repeats and the age of death. However, also at a younger age, the premutation might affect brain function. A recent study in female carriers showed a poorer performance on a magnitude comparison task with increasing repeat length from 67 to 150 [49]. It is not clear whether this is the result of the increased amount of mRNA or of the assumed reduction in FMRP associated with increasing repeat length. In contrast to the absence of mRNA and FMRP seen in fragile X syndrome, carriers of premutation alleles have a marked two-fold to eight-fold increase in mRNA levels despite normal or slightly reduced FMRP levels [50,51]. A leading hypothesis for why premutations cause disease is that the elongated CGG repeat binds and sequesters important proteins within nuclear inclusions, preventing them from performing their normal functions [52]. In a human neural cell culture system, a lower threshold for toxicity appears to be between 62 and 95 CGG repeats [53]. A clear negative correlation between mRNA concentration and cell viability was seen for repeat sizes of 95 CGG repeats and above. Other cell types may also be damaged by the premutation. Nuclear laminin and the transcriptional induction of several stress response genes were dysregulated in both skin fibroblasts and neurons, pointing out that the toxic effects of the expanded CGG repeat are not restricted to the central nervous system [54•]. Further studies are needed to investigate whether the fibroblast can serve as a peripheral cell model of FXTAS and whether abnormality in this tissue might be an early indicator of FXTAS.

The pathogenicity of the premutation may even begin before or at birth. Premutation knockin mice displayed abnormal dendritic arborization and reduced longevity in cultured hippocampal neurons [55]. These observations led to the conclusion that the clinical features seen in carriers might be attributable to an early developmental component of *FMR1* mRNA associated toxicity. This hypothesis was further strengthened by observations that neuronal migration is impaired in the embryonic cerebral cortex of premutation mice [56•]. These findings are relevant in exploring treatment strategies appropriate for infant carriers of the premutation. However, these results contrast with findings in a second, independently generated premutation mouse model. In this premutation model, behavioural deficits similar to the ones observed in fragile X mice were observed, albeit milder, which is consistent with the phenotype in humans [57]. In concordance with this behavioural phenotype, they detected reduced FMRP levels up to only 15–20% of wild-type levels [58]. Moreover, the authors found an increased number of spines in combination with diminished dendritic branching in cultured neurons, making the authors believe that it would be more reasonable to state that the phenotypic effects seen in this model are the consequence of the decreased

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concentration of FMRP rather than due to the mRNA toxicity.

In a *Drosophila* model of FXTAS, histone deacetylases (HDAC) were shown to suppress CGG repeat induced neurodegeneration [59•]. These findings made the authors look at the acetylation status of the premutation carriers, and they saw an increased acetylation of the histones at the d*Fmr1* locus. In concordance with these observations, histone acetyltransferase (HAT) inhibitors repress *Fmr1* mRNA expression in premutation cell lines. The authors put selective HATs and HDACs forward as potential therapeutics in FXTAS.

Conclusion

Twenty years of research on *FMR1*-related disorders has led to surprising discoveries. The premutation, long thought of as having no clinical effect, is now associated with multiple disorders. The number of pathways that FMRP is modulating keeps growing. Interestingly, several of these pathways are amenable to treatment. Several studies in animal models and even pilot studies in patients, initially aimed at improving the behavioural symptoms in the FXS, raise hope for targeted treatment in the near future.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 701–702).

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