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Fragile X Syndrome: From Pathophysiology to New Therapeutic Perspectives

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1. Introduction

In the present chapter we will provide an overview of recent literature regarding new therapeutic perspectives in Fragile X syndrome (FXS), which are based on a rational approach well-grounded on a deeper understanding of the disease pathophysiology. FXS represents a paradigmatic example of how research can be translated into therapy targeting dysfunctional mechanisms rather than symptoms. Several clinical trials using these new strategies are underway. Here, we will mainly describe the basic mechanisms and the animal studies which suggest the use of these innovative pharmacological approaches. In addition, an emerging concept is that developmental pathologies with intellectual disability (ID) presenting common features such as autism, behavioural disturbances and epilepsy might share dysregulation of the same biochemical pathways. The identification of common altered pathways in ID might help to develop new therapeutic strategies helpful for apparently diverse pathologies.

2. Fragile X syndrome

2.1 FXS: Clinic and genetics

ID, also referred with the term Mental Retardation, is the most common developmental disorder, with a prevalence of 1-3%, and includes a highly diverse group of cognitive disorders. It is defined, according to the American Psychiatric Association, by an intelligence quotient (IQ) of 70 or below, and deficits in at least two behaviours related to adaptive functioning diagnosed by 18 years of age. Gene defects account for about half of all patients and mutations have been identified in more than 400 genes, of which 97 are positioned in the X chromosome (reviewed in Kaufman et al., 2010).

FXS is an X-linked developmental disorder which represents the most common form of inherited ID, affecting approximately 1 in 2500-6000 males and 1 in 4000-8000 females. ID ranges from severe to mild and may be associated with Attention Deficit and/or Hyperactive Disorder (ADHD), autism, behavioral disturbances, hyperactivity, seizures and hypersensitivity to sensory stimuli. People with FXS may also exhibit facial dysmorphic

features including a long face with prominent ears and arched palate, hyperextensible joints, mitral valve prolapse and macroorchidism (R.J. Hagerman, 2002).

The most common genetic defect in FXS is a CGG trinucleotide repeat expansion of >200 repeats in the 5' untranslated region of the FMR1 (fragile X mental retardation 1) gene, located on the long arm of the X chromosome at position 27.3 (Verkerk et al., 1991). This triplet amplification is associated to methylation of the FMR1 promoter region and transcriptional silencing of the FMR1 gene with consequent loss or significant reduction of the FMR1 encoded protein FMRP (fragile X mental retardation protein) (Devys et al., 1993; O'Donnel & Warren, 2002). Expansions of CGG repeats are unstable during meiosis, increasing in length from one generation to the next. In carriers of the premutation, the expansion is between 55–200 repeats (normal is <45), and does not result in FMR1 methylation and loss of FMRP expression, but gives rise to two independent pathologies such as fragile X-associated tremor/ataxia syndrome (FXTAS) and premature ovarian failure, primarily in males and females respectively (reviewed in Berry-Kravis et al., 2007; P.J. Hagerman et al., 2008; Toniolo, 2006). It has been hypothesised that these conditions are caused by a gain of function toxic effect of increased levels of CGG repeat-containing FMR1 mRNA reviewed in (reviewed in Berry-Kravis et al., 2007), although decreased levels of FMRP may also play a role (Qin et al., 2011).

2.2 FXS: Alterations of dendritic spine morphology

Microscopic analysis of brain material from both patients with FXS and mouse models of the disease reveals no gross morphological abnormalities (Bakker et al., 1994; Reyniers et al., 1999). However, in certain brain areas such as cortex and hippocampus, long and thin dendritic spines have been observed, consistent with an immature spine phenotype (Comery et al., 1997; Irwin et al., 2001, 2002; Nimchinsky et al., 2001).

Dendritic spines are protrusions of dendritic membrane and serve as the postsynaptic component for the vast majority of central nervous system (CNS) excitatory synapses. Spines are dynamic structures that can regulate many neurochemical events related to synaptic transmission and modulate synaptic efficacy. The tip of the spine contains an electron-dense region, the "postsynaptic density" (PSD), that is a protein-dense specialization and consists of receptors, channels, and signaling proteins involved in synaptic transmission. Spines are highly motile structures, their density varies across areas of different brain regions but also within individual dendritic trees; spine morphology changes with development and requires actin cytoskeleton remodelling and local protein translation in response to synaptic activity. Notably, spines are equipped with translational machinery and protein synthesis may occur in response to receptor activation. The structural modifications of spines are correlated with synaptic plasticity (see below); Long Term Depression (LTD) is generally associated with a shrinkage of spines, whereas Long Term Potentiation (LTP) causes formation of new spines and enlargements of existing spines (Tada & Sheng, 2006).

Abnormalities in dendrites and spines have been implicated in several psychiatric disorders and have been associated with cognitive impairment and mental retardation disorders (Tuberous Sclerosis Type I, Fetal alcohol syndrome, Down syndrome, Rett syndrome, autism and FXS) (Nimchinsky et al., 2002), but the causes of these malformations are not yet well understood.

2.3 FMRP: Expression, structure and interacting proteins

FMRP is an RNA binding protein involved in the regulation of target mRNA translation and transport. It belongs to a small family of highly conserved RNA binding proteins referred to as the fragile X-related (FXR) proteins; it is expressed in several tissues and organs and has been found to be most abundant in the brain and testis. FMRP is highly expressed in neurons and is associated with translating polyribosomes and ribonucleoprotein complexes (mRNP) in the cytoplasm, in dendrites and dendritic spines where it is believed to regulate mRNA translation (De Diego Otero et al., 2002). Recent data also suggest that FMRP is present in axons and pre-synaptic terminals (Christie et al., 2008).

The analysis of the structure of FMRP has revealed the presence of different functional motifs and has contributed to elucidate the function of the protein. FMRP contains three different RNA binding domains: two hnRNP K-protein homology (KH) domains and an Arg-Gly-Gly (RGG) box (Siomi et al., 1993), which bind sequence-specific elements such as the U-rich sequences called FMRP kissing complex and G-quartet, respectively (Darnell et al., 2001, 2005). Interestingly, a missense mutation in the second hnRNP KH binding domain (I304N) abolishes FMRP association with polyribosomes and causes FXS. The presence within FMRP of a nuclear localization signal (NLS) and a nuclear export signal (NES) suggests that FMRP is a shuttle protein and that it travels between the nucleus and the cytoplasm (Darnell et al., 2001, 2005; Eberhart et al., 1996). In the nucleus, FMRP binds to RNAs and proteins to form the mRNP particle and is then exported to the cytoplasm where it could associate with translating ribosomes (Corbin et al., 1997; Eberhart et al., 1996; Feng et al., 1997a; Khandjian et al., 1996). The mRNP complex can stay in the neuronal cell body or it can move to the dendritic spines via the microtubule structures present in the dendrites. In this way, FMRP can control the local protein synthesis at the synapses, influencing synaptic function, structure and plasticity (Bardoni et al., 2006; Feng et al., 1997b; Miyashiro et al., 2003; Zukin et al., 2009).

The structure of FMRP presents also two coiled coil (CC) domains involved in protein-protein interactions. Using immunoprecipitation two-hybrid screens or large mass spectrometry analysis several FMRP interacting proteins have been identified including its two close paralogs, FXR1P and FXR2P (Fragile X Related Protein 1/2), NUFIP1 (Nuclear FMRP Interacting Protein 1), 82-FIP (82 kDa-FMRP Interacting Protein) and the two closely related proteins CYFIP1 and CYFIP2 (Cytoplasmic FMRP Interacting Protein 1/2). The role and importance of these interacting proteins in the function of FMRP is not clear; it is possible that the interaction with these proteins might modulate the function of FMRP in different cellular compartments (reviewed by Bardoni et al., 2006).

FXR1P and FXR2P show a similar structure to that of FMRP, being characterized by the presence of two KH and one RGG box RNA binding domains and nuclear localization and export signals (NLS and NES). In the absence of FMRP there is not a compensatory increase in levels of FXR1P and FXR2P, which would suggest functional redundancy. However, the precise role of the two FMRP paralogs and their reciprocal interaction is still under investigation.

CYFIP1 and CYFIP2 are highly homologous to each other; CYFIP2 interacts with all members of the FXR family, while CYFIP1 is specific for FMRP (Schenck et al., 2003). CYFIP1 and 2 are localized at synapses and CYFIP1 also interacts with activated Rac1 (Kobayashi et al., 1998; Schenck et al., 2003), a small RhoGTPase involved in maturation and

maintenance of dendritic spines (Govek et al., 2005), suggesting that FMRP might influence cytoskeleton remodelling through Rho/Rac GTPase (Schenck et al., 2003). The interaction between FMRP and CYFIP1 has been proposed to mediate the inhibition of translation initiation by sequestering the cap-binding protein eIF4E (Napoli et al., 2008).

2.4 FMRP: Regulation of target mRNA translation and transport

There is a general consensus that FMRP acts mainly as a negative regulator of translation although the underlying mechanisms are not clear. Several mechanisms have been proposed and they may not be mutually exclusive. The majority of co-sedimentation studies has found an association of FMRP with polyribosomes and suggests that FMRP acts by repressing elongation (reviewed by Bardoni et al., 2006), although other studies suggest that FMRP is associated with BC1 (a non translatable RNA), a complex which will block the initiation step through an interaction with eIF-4E-BP and CYFIP1 (Napoli et al., 2008). FMRP has been found also associated to high-density granules, which represent ribonucleic aggregates where mRNA translation is stalled (Aschrafi et al., 2005). A recent work supports a model in which FMRP acts to stall ribosomal translocation during elongation; although the exact mechanism by which FMRP stalls ribosomes remains to be determined, authors suggest that it is a dynamic and reversible mechanism related with plastic changes occurring both in the cytoplasm and at synapses (Darnell et al., 2011). Another mechanism by which FMRP might control expression levels of proteins is through the regulation of transcript stability, such as that of microRNA-124a (miRNA-124a) and PSD-95 (Xu et al., 2008; Zalfa et al., 2007). A further element of complexity is added by recent data suggesting that FMRP may also promote translation of target mRNAs, such as Trailer-Hitch and Superoxide Dismutase 1 (SOD1) transcripts (Bechara et al., 2009; Monzo et al., 2006). Thus, the translation and expression of FMRP targets can be either positively or negatively affected by FMRP expression, indicating that the potential role of FMRP as a translational regulator is much more complex than it was originally believed.

In addition to its role as a regulator of translation FMRP has been involved in the regulation of RNA transport along dendrites. A number of putative RNA targets have been found to be abundantly expressed in dendrites, although no major changes have been detected in the steady-state distribution and expression levels in the absence of FMRP (Bassel & Warren, 2008). FMRP traffics in the form of motile "RNA granules", structures different in size and composition containing translationally repressed mRNP complexes which travel on microtubules to the dendrites. mRNAs, once localized to the appropriate sites, are released from granules and translated in response to appropriate stimuli (reviewed in Bassel & Warren, 2008). FMRP trafficking is regulated in response to activation of group-I metabotropic glutamate (mGlu) receptors. Application of 3,5-Dihydroxyphenylglycine (DHPG), a selective agonist of group-I mGlu receptors, enhances the dendritic transport of several FMRP target mRNAs, including those encoding FMRP, Map1b, CaMKII in hippocampal cultured neurons (Antar et al., 2004; Dichtenberg et al., 2008; Ferrari et al., 2007). Dichtenberg shows that FMRP, upon DHPG stimulation, interacts more efficiently with the kinesin light chain and this mGlu-receptor mediated transport is markedly attenuated in the absence of FMRP. These data suggest that FMRP is involved in promoting the activity-dependent localization of bound mRNAs, but not in the constitutive transport of mRNAs in dendrites.

It is clear that, as a consequence of the lack of FMRP, levels of several synaptic and non-synaptic proteins are altered and key biochemical pathways might be dysregulated in FXS.

The *in vivo* evidence that an overall increase of protein synthesis in several brain regions occurs in FXS has been provided by quantitative autoradiographic studies using radioactively labelled aminoacid L-[1-¹⁴C]leucine, which showed an increase in several regions of Fmr1 knock out (KO) mice compared to wild type (WT) (Qin et al., 2005). Accordingly, Dölen and collaborators have shown a 20% increase protein synthesis in hippocampal slices of Fmr1 KO mice compared to WT using ³⁵S-methionine/cystine labelling (Dölen et al., 2007). These studies corroborate the view that FMRP acts mainly as inhibitor of protein synthesis in the brain, although do not exclude the possibility that certain proteins might be downregulated in a direct or an indirect way as a result of dysregulated pathways.

The identification of target mRNAs has been object of intense research during the last years, using a variety of *in vitro* assays. A recent work has identified 842 FMRP mRNA targets using a stringent high-throughput sequencing-cross-linking immunoprecipitation (HITS-CLIP) method (Darnell et al., 2011). An overlap has been found with a list of FMRP mRNA targets previously identified with a co-immunoprecipitation method (181 mRNAs) (V. Brown et al., 2001), but a significant number of mRNAs are newly identified. Interestingly, this list includes several well-studied autism candidate genes such as NLGN3, NRXN1, SHANK3, PTEN, TSC2 and NF1 and components of pre- and post-synaptic compartments.

2.5 FXS animal models

A major advancement towards a better understanding of the molecular mechanisms implicated in FXS is represented by the development of FXS animal models, which have been also used for pre-clinical studies aimed at testing potential therapeutic interventions. Mouse and *Drosophila melanogaster* are the main genetic model organisms used to these purposes. The mouse Fmr1 gene and its two related genes Fxr1 and Fxr2 are well conserved relative to their human homologs FMR1, FXR1 and FXR2, respectively (Bakker et al., 1994; Bontekoe et al., 2002; Mientjes et al., 2004), whereas the fly model organism has a single FMR1 homolog (dFmr1) that is more functionally similar to human FMRP than to human FXR1 or FXR2 (Coffee et al., 2010). Both the fly and the mouse models present phenotypic abnormalities that are similar to those observed in humans such as: behavioural changes, altered axon morphology and connectivity, social, memory and learning deficits. The Fmr1 KO mouse shows macroorchidism, hyperactivity, a mild spatial learning impairment in the Morris water maze (Bakker et al., 1994), abnormalities in dendritic spines (Comery et al., 1997; Nimchinski et al., 2001) and altered synaptic plasticity (see below). Fmr1 KO mice have also an increased susceptibility to audiogenic seizures (AGS) (Musumeci et al., 2000), which is specifically reverted by the introduction of constructs codifying the human FMR1 gene (Musumeci et al., 2007). In addition, Fmr1 KO mice is currently considered one of the leading animal models of autism (Bernardet & Crusio, 2006).

To study the function of FXR2P and FXR1P and their possible implication in FXS, Fxr1 and Fxr2 KO mouse models have been generated. Homozygous Fxr1 KO neonates die shortly after birth for cardiac or respiratory failure; whereas a mouse model expressing very low levels of FXR1P displays a strongly reduced limb musculature and has a reduced life span, suggesting a role for FXR1P in muscle mRNA transport/translation control similar to that seen for FMRP in neuronal cells (Mientjes et al., 2004).

Fxr2 KO mice do not show gross abnormalities in brain or testis, but are hyperactive in the open-field test, have reduced levels of prepulse inhibition, display less contextual

conditioned fear and are less sensitive to a heat stimulus. Interestingly, *Fxr2* KO mice present some behavioural phenotypes similar to those observed in *Fmr1* KO mice (Bontekoe et al., 2002).

A double *Fmr1/Fxr2* KO mouse has also been created. These mice have exaggerated behavioural phenotypes in open-field activity, prepulse inhibition of acoustic startle response and contextual fear conditioning when compared with *Fmr1* KO mice, *Fxr2* KO mice or WT (Spencer et al., 2006). This is in line with the hypothesis that *Fmr1* and *Fxr2* play a similar role in pathways controlling locomotor activity, sensorimotor gating and cognitive processes. In addition, *Fmr1/Fxr2* double KO mice exhibit more severe electrophysiological alterations than either single KO model, which suggests that FMRP and FXR2P regulate synaptic plasticity both together and separately (J. Zhang et al., 2009).

2.6 Role of FMRP in the formation of neuronal network

Although FXS has traditionally been thought of as a disorder of the postsynaptic compartment, several evidences suggest a potential axonal or pre-synaptic role for FMRP. The first evidence that suggests a pre-synaptic role for FMRP was the observation that FMRP is present in growth cones of developing axons and distal segments of mature axons in hippocampal cell cultures (Antar et al., 2006). More recently, FMRP (but also FXR1P and FXR2P) have been detected in pre-synaptic terminals in discrete small structures defined as granules (Fragile X granules) by light and electron microscopy in brain slices (Christie et al., 2009). The expression of such pre-synaptic FMRP granules is regulated both developmentally and regionally in the brain, being maximal in the frontal cortex and hippocampal area CA3 in two-weeks-old mice but virtually non-existent in adult neocortex or in CA1 (Christie et al., 2009). A second line of evidence comes from studies in *Drosophila*, where mutations in the *Fmr1* gene result in axonal defects. It has been demonstrated that in *Drosophila* loss of dFMRP causes defects in axonal targeting and arborization (Y.Q. Zhang et al., 2001), misregulated pre-synaptic structure (Michel et al., 2004), neuromuscular junction (NMJ) synapse overelaboration (overgrowth, overbranching, excess synaptic boutons), and altered neurotransmission (Gatto & Broadie, 2008). Two recent papers in *Drosophila* highlights the role of FMRP in activity-dependent axon pruning and in regulation of synaptic structure during development (Gatto & Broadie, 2008; Tessier & Broadie 2008). Using the *Drosophila* model these authors addressed the question whether FXS is mainly a disease of development, characterized by structural defects, or a disease of plasticity, or both. The establishment of neural circuits proceeds via a two-stages process: an early, activity-independent wiring to produce a rough map characterized by excessive synaptic connections and subsequent, use-dependent pruning to eliminate inappropriate connections and reinforce maintained synapses. dFMRP expression and function are maximal during late-stage periods of axon pruning, which requires both dFMRP and sensory input activity. dFMRP has a primary role in activity-dependent neural circuit refinement during late brain development (Tessier & Broadie, 2008). Gatto and Broadie (2008) observed that constitutive neuronal dFMRP expression rescues all NMJ synaptic structural defects, demonstrating a strictly pre-synaptic dFMRP requirement. By contrast, targeted pre-synaptic dFMRP expression does not rescue neurotransmission function in the null mutant, indicating a separable post-synaptic dFMRP requirement. Temporally, transient early-development expression of dFMRP strongly rescues synaptic architecture, demonstrating primarily an early role for dFMRP in establishing synapse morphology.

Interestingly, acute dFMRP expression at maturity weakly rescues synaptic structure defects, showing that late-stage intervention might only partially compensate for structural abnormalities established early during development. Thus, FMRP may play a double crucial role by regulating the structure of neural circuits during development and by regulating synaptic plasticity during maturity.

Recent data in the mouse model also suggest that FMRP might be involved in the establishment of neuronal connectivity, possibly through mechanisms which involve guidance and stabilization of axons during development (Bureau, 2009). Bureau et al. (2008) investigated the development of excitatory projections in the barrel cortex of *Fmr1* KO mice and they observed that projections are altered both functionally and morphologically, suggesting an important role for FMRP in this process. Dysregulated neuronal connectivity in the barrel cortex causes defective glutamatergic synapse maturation, delayed and aberrant formation of sensory maps, and altered synaptic plasticity during the critical period (Harlow et al., 2010). In general, the absence of FMRP could lead to altered network synchrony and hyperexcitable neuronal networks (Chuang et al., 2005; Gibson et al., 2008).

These data have a very strong implication for the therapeutic approach to FXS, but also to other developmental disorders characterized by altered neuronal connectivity. Interestingly, in a list of newly identified FMRP mRNA targets several transcripts encode for pre-synaptic proteins and are implicated in autism spectrum disorders (Darnell et al., 2011). It will be important in the future to establish whether a therapeutic intervention is able to rescue these early established abnormalities in neuronal circuitry.

3. Therapeutic strategies in FXS

Current therapeutic approach to patients with FXS is aimed at correcting symptoms or behavioural deficits, including hyperactivity and anxiety. Medications include stimulants, antipsychotics, anti-depressants and anticonvulsants. Patients with FXS also seem to benefit from behavioural intervention and special educational programs. As demonstrated in the FXS mouse model, an enriched environment can improve behaviour, and thus this therapy might also be beneficial for patients (Restivo et al., 2005).

In the last few years the amount of scientific publications in the field of neurobiology of FXS have exponentially increased and these efforts have led to important discoveries which are now partially translated in therapeutic perspectives. These include the use of drugs to correct the abnormal activity of the mGlu receptor- and GABA-pathways. In addition, novel therapeutic targets will be discussed based on other pathways, which have been found to be dysregulated in mouse models of FXS.

3.1 mGlu5 receptor: A key protein for synaptic plasticity

Glutamate, the major excitatory neurotransmitter in the mammalian CNS, exerts its action by interacting with ionotropic (iGlu) and mGlu receptors. iGlu receptors are multimeric ion channels responsible for fast synaptic transmission and are subdivided into three distinct subtypes: AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), kainate, and NMDA (N-methyl-D-aspartate) receptors. mGlu receptors are members of a G-protein-coupled receptor superfamily that includes GABA_B, Ca²⁺ sensing, some taste and pheromone receptors (Bockaert & Pin, 1999).

The family of mGlu receptors comprises eight subtypes (mGlu1-mGlu8) that are divided into three distinct groups on the basis of sequence similarities and different pharmacological responses. Group-I includes mGlu1 and mGlu5 receptor subtypes which are coupled to G_q/G_{11} proteins and whose activation stimulates polyphosphoinositide (PI) hydrolysis and an increase in intracellular Ca^{2+} release as a result of a PKC-mediated receptor phosphorylation (Kawabata et al., 1996). Activation of group-I mGlu receptors also stimulates the ERK1/2 MAP kinase and the phosphatidylinositol-3-kinase (PI3K) pathways, which are involved in cell proliferation, differentiation, and survival, as well as in processes of activity-dependent synaptic plasticity (Ferraguti et al., 1999; Peavy & Conn, 1998; Rong et al., 2003). Activation of ERK in striatum and PI3K in hippocampus (Mao et al., 2005; Rong et al., 2003) requires the interaction of group-I mGlu receptors with Homer proteins, a class of scaffolding proteins cross-linking group-I mGlu receptors (mGlu1 and mGlu5) to inositol triphosphate (IP_3) receptors and to other proteins of the post synaptic density such as SHANK (Tu et al., 1998, 1999). Homer proteins also control several functions of group-I mGlu receptors such as constitutive activity (Ango et al., 2001), cell surface expression and trafficking (Ango et al., 2002; Coutinho et al., 2001), lateral mobility (Sergé et al., 2002) and coupling to ion channels of the cytoplasmic membrane (Kammermeier et al., 2000). Group-II and group-III include mGlu2/3 and mGlu4,6,7,8, respectively and are coupled to G_i/G_o proteins. While mGlu1 and mGlu5 receptors are generally found in postsynaptic densities and modulate postsynaptic efficacy, mGlu2, -3, -4, -7, and -8 receptors are mainly (but not exclusively) pre-synaptic and regulate neurotransmitter release (Luján et al., 1997; Schoepp, 2001). The pharmacology of mGlu receptors has expanded in the last years and ligands for mGlu receptors are now considered the most promising drugs in the treatment of neurological and psychiatric disorders (reviewed by Nicoletti et al., 2011). Here we will focus on group-I mGlu receptors, namely mGlu5, for their implication in the pathophysiology of FXS.

mGlu1 and mGlu5 receptors have a different temporal and regional expression pattern. While the transcript of mGlu1 receptors is low at birth and progressively increases during postnatal development, the transcript of mGlu5 receptors is highly expressed early after birth and progressively decreases afterwards (Catania et al., 1994). Expression of mGlu5 receptors is high and widespread in the first two weeks of postnatal life (reviewed in Catania et al., 2007) when the PI response to group-I mGlu receptor agonists in brain slices is substantial (Nicoletti et al., 1986a, 1986b). A much lower receptor response is detected in hippocampal, cortical or striatal slices of adult rats, where only agonists endowed with high intrinsic efficacy can stimulate PI hydrolysis (Nicoletti et al., 1986a, 1986b). The mGlu1a receptor protein is highly expressed in discrete regions of the adult brain including the cerebellum, olfactory bulbs, thalamus and pars compacta of the substantia nigra, and is barely detectable during early development (Lopez-Bendito et al., 2002). These expression studies suggest that mGlu5 receptors may have an important role in plastic changes occurring early during post-natal development (Catania et al., 2007).

Most of group-I mGlu receptors are located in dendritic spines (Baude et al., 1993), in an annulus that circumscribes the PSD, but some (probably mGlu5) are also distributed on glutamatergic nerve terminals (Cochilla & Alford, 1998; Gereau & Conn, 1995; Rodriguez-Moreno et al., 1998; Sistiaga et al., 1998). mGlu5 receptors are also expressed in non-neuronal cells, including astrocytes, oligodendrocytes and microglia, stem progenitor cells, and a variety of peripheral cells (Nicoletti et al., 2011).

mGlu5 receptors are involved in the regulation of synaptic plasticity, including the induction of LTP (important for retaining nascent synapses) and LTD (important for activity-guided synapse elimination), two electrophysiological substrates that, working in concert, contribute to learning and memory storage throughout postnatal life (Bear, 1998). LTP is a long term increase in synaptic efficacy and is associated with the strengthening of the connection between a pre-synaptic and post-synaptic neuron, whereas LTD is defined as the weakening of the synapse, and is mainly reflected by a reduced number of iGlu responsive AMPA receptors at the post-synaptic membrane (Collingridge et al., 2010). Activation of mGlu5 receptors is involved in both LTP and LTD. Mice lacking mGlu5 receptors show impaired learning and reduced LTP in the hippocampal CA1 region (Lu et al., 1997).

There are two forms of LTD: one is dependent on activation of post-synaptic NMDA receptors, the other requires activation of post-synaptic group-I mGlu receptors (Oliet et al., 1997) and also can be readily induced by the selective group-I mGlu receptors agonist DHPG (Huber et al., 2001; Palmer et al., 1997). Both types of LTD determine a decrease in the number of post-synaptic AMPA receptors by distinct mechanisms (Bear et al., 2004). One important distinction is that LTD triggered by mGlu receptor activation (mGlu-LTD), but not NMDA-receptor-dependent LTD, requires the activation of mGlu5 receptors and the rapid translation of pre-existing mRNAs in the post-synaptic dendrites through a mechanism that involves ERK phosphorylation (Gallagher et al., 2004).

3.2 mGlu5 receptor: A pharmacological target in FXS

The first indication for a link between mGlu receptors and FXS was the evidence that activation of group-I mGlu receptors in rat and mouse brain synaptoneurosome stimulates the rapid translation of pre-existing mRNAs, including the FMRP mRNAs (Weiler et al., 1997, 2004). Since, a growing number of studies was carried out to support a role of group-I mGlu receptors in the pathophysiology of FXS. In particular, the finding that mGlu5-/protein synthesis-dependent forms of synaptic plasticity, namely mGlu5-dependent LTD, are increased in the mouse model of FXS led Bear and collaborators to formulate the “mGlu theory” of FXS, which postulates that in the absence of FMRP, which acts reducing the mGlu5-activated mRNA translation at synapse, levels of FMRP-regulated proteins are increased and, as a consequence, can be reduced by mGlu5 pharmacological antagonism (Bear et al., 2004). Other forms of synaptic plasticity, including the more classical NMDA-receptor dependent LTD, show no abnormalities in the hippocampus of *Fmr1* KO mice. Another important step towards the understanding of FXS physiopathology was represented by the finding that, while in WT mice mGlu5-dependent LTD is blocked by inhibitors of protein synthesis, this is not the case in *Fmr1* KO mice, suggesting that in the absence of FMRP LTD proteins are constitutively and highly expressed before LTD induction (Waung & Huber, 2009).

Thus, the absence of FMRP causes an abnormal expression of dendritic proteins leading to the amplification of mGlu-mediated long-term responses. The identification of these proteins, which may be critical for the pathophysiology of synaptic dysfunction in FXS, is crucial. Some proteins encoded by FMRP target mRNAs may play a role. For example, Map1b interacts with the GluR2 interacting protein and scaffold GRIP1 (Davidkova & Carroll, 2007; Seog, 2004). Other proteins which are rapidly synthesized after mGlu5 receptor activation and that are basally elevated in *Fmr1* KO mice include CaMKII (Zalfa et

al., 2003), amyloid precursor protein (APP), Arc/Arg3.1 (Park et al., 2008; Zalfa et al., 2003) which are all involved in mechanisms underlying synaptic plasticity. The list of FMRP mRNAs targets has recently grown with the discovery of 842 mRNA by using the high stringent CLIP method (Darnell et al., 2011). Further studies examining the expression levels of the encoded proteins in FXS and their regulation by mGlu receptors may corroborate the link between mGlu5 activation and protein synthesis of FMRP target mRNAs and its role in synaptic plasticity under physiological and pathological conditions. In addition, as a direct or indirect consequence of altered protein synthesis at synapses, several mGlu-mediated signalling pathways might be dysregulated. Interestingly, mGlu5 receptors in *Fmr1* KO mice are less tightly associated to Homer proteins (Giuffrida et al., 2005), which suggests either an increase of mGlu5 constitutive activity or an altered coupling of mGlu5 receptors with downstream signalling pathways. Accordingly, Ronesi and Huber (2008) reported that induction of PI3K-Akt-mTOR signalling by mGlu5 is impaired in *Fmr1* KO mice and, differently than in WT mice, mGlu5 dependent LTD is insensitive to disruption of mGlu5/Homer interaction. Further studies are needed to understand how the lack of FMRP affects mGlu5 mediated responses in FXS.

Several pharmacological studies have supported the “mGlu theory”, by demonstrating that phenotypic features of FXS can be corrected with the use of antagonists of mGlu5 such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and fenobam. MPEP is a systemically active negative allosteric modulator of mGlu5 receptors and can also inhibit constitutive activity of mGlu5 acting as an inverse agonist (Yan et al., 2005). Fenobam, which had previously been investigated as an anxiolytic, has been identified as a highly potent, selective negative modulator of mGlu5 receptor (Porter et al., 2005). In particular, MPEP blocks audiogenic seizure susceptibility of *Fmr1* KO mice (Chuang et al., 2005) and both MPEP and fenobam restore dendritic spine morphology in hippocampal cell cultures from *Fmr1* KO mice (De Vrij et al., 2008).

A more direct evidence that the “mGluR theory” might be corrected has been provided using genetic interaction experiments (Dölen et al., 2007). In this study, *Fmr1* KO mice were crossed with heterozygous mGlu5 receptor KO mice generating double mutants of *Fmr1* and *Grm5* (the gene that encodes mGlu5 receptor) and multiple phenotypes relevant to the pathogenesis of FXS were examined. Reduction of mGlu5 expression by 50% in the *Fmr1* KO/*Grm5* heterozygote cross rescued altered ocular dominance plasticity, increased density of dendritic spines, increased basal protein synthesis, exaggeration of avoidance extinction and audiogenic seizure susceptibility, but not macroorchidism (Dölen et al., 2007). Moreover, no change in protein synthesis was detected in *Grm5* heterozygote, suggesting that a therapeutic dose of an mGlu5 receptor antagonist for FXS patients should not have negative side effects in unaffected individuals. These pre-clinical studies support the therapeutic utility in FXS patients. Interestingly, the potential use of mGlu5 antagonists is not restricted to FXS but is considered for a variety of human conditions including anxiety, convulsions, pain, depression, Parkinson's disease and gastroesophageal reflux disease (see Nicoletti et al., 2011).

An initial small pilot open label, single dose trial with fenobam in adults with FXS did not reveal any adverse effect and produced promising results showing an improvement of prepulse inhibition (Berry-Kravis et al., 2009). More recently, the Novartis compound AFQ056 has been used in a randomized, double-blind study in 30 male FXS patients aged 18-35 years. Although an initial assessment did not show any improvement after treatment,

when patients were divided into two groups on the basis of a full or partial methylation of the FMR1 promoter a significant improvement on stereotypic behaviour, hyperactivity and inappropriate speech were detected only in the full methylation group (Jacquemont et al., 2011). While this work confirms the clinical efficacy of mGlu5 pharmacological blockade in FXS, there is no clear explanation for the lack of improvement in patients with partial methylated FMR1 gene. More clinical studies in a higher number of patients are needed.

3.3 GABA system as target of viable pharmacological treatments in FXS

In addition to the mGlu receptors, several evidences suggest that gamma-aminobutyric acid (GABA) signalling is another molecular pathway involved in FXS. Expression and functional studies suggest that defects in GABA transmission might be region specific and might involve different components of the GABAergic system in different brain regions.

GABA is the major inhibitory neurotransmitter in the CNS and plays a key role in modulating neuronal activity, by maintaining the inhibitory tone and the physiological balance between inhibition and excitation at synapses. GABA mediates its action via two distinct receptor systems, the ionotropic GABA_A and metabotropic GABA_B receptors.

Ionotropic GABA_A receptors are heteropentameric complexes, formed by the assembly of various classes of at least 19 different subunits (α 1-6, β 1-3, γ 1-3, δ , ϵ , θ , π and ρ 1-3) (Simon et al., 2004) associated with channels permeable to Cl⁻ ions. In brain, a high diversity of GABA_A receptor subtypes having a spatio-temporal specific distribution in different regions has been found (Barnard et al., 1998; Kneussel, 2002; Korpi et al., 2002). The subunit combination confers highly different pharmacological and physiological properties to GABA_A receptors (Fritschy et al., 1995).

GABA_B receptors are heterodimeric G protein-linked receptors constituted by two different subunits. They have a pre- and post-synaptic distribution; at pre-synaptic level they can inhibit the release of neurotransmitters through a decrease of Ca²⁺ entry, whereas, at post-synaptic level they reduce neuronal excitability through an increase of K⁺ conductance. In general, they mediate a slower and more prolonged inhibitory signal than GABA_A receptors (Bormann, 2000; Chebib et al., 1999). Interestingly, GABA_B receptors agonists inhibit pre-synaptic glutamate release and consequently the post-synaptic glutamate responses (reviewed in Chalifoux & Carter, 2011).

An important indication that the GABAergic system might be involved in FXS was the evidence, obtained using the Antibody Positioned RNA Amplification (APRA) technique, that the mRNA of the δ subunit of the GABA_A receptor is directly bound to FMRP (Miyashiro et al., 2003). In Fmr1 KO mouse changes in levels of expression of both GABA_A and GABA_B receptors have been found by different authors. Several studies have revealed in different brain regions, all playing an important role in cognitive functions (behaviour, learning, memory and anxiety), as cortex, hippocampus, diencephalon and brainstem an under expression of many distinct GABA_A receptor subunits (α 1, α 3, α 4, α 5 β 1 and β 2 and γ 1 and γ 2 and δ) at the mRNA (Curia et al., 2009; D'Hulst et al., 2006; Gantois et al., 2006) and protein level (Adusei et al., 2010; El Idrissi et al., 2005).

Altered GABA transmission has been reported in different brain regions. An alteration of both GABAergic and cholinergic system, with a lower inhibitory effect mediate by GABA_A receptor in subiculum neurons has been detected by electrophysiology in brain slices of

Fmr1 KO mice (D'Antuono et al., 2003). More recently, other electrophysiological findings in subiculum have shown that tonic GABA_A currents were down regulated in Fmr1 KO mice, whereas no significant differences were observed in phasic currents (Curia et al., 2009). An increased GABA transmission has been found in the striatum (Centonze et al., 2008), whereas a robust reduction in the inhibitory transmission has been revealed in the amygdala, which results in hyper-excitability of principal neurons and is likely due to pre-synaptic defects such as decreases in GABA production and release (Olmos-Serrano et al., 2010). Accordingly, a reduction of GABA has been detected in Fmr1 KO mice using a metabolomic approach (Davidovic et al., in press).

Furthermore, cytoarchitectonic and morphological studies from somatosensory cortex highlighted a significant reorganization of neocortical inhibitory circuits of GABAergic interneurons in the Fmr1 KO mouse. In fact, this animal model showed a marked reduction of parvalbumin-positive neurons compared to the WT mice, whereas no difference was observed for calbindin- and calretinin-positive neurons (Selby et al., 2007).

Thus, most expression and functional data suggest that increasing GABAergic transmission might result in a beneficial effect, at least in certain regions. Accordingly, experiments from Fmr1 mutant *Drosophila* have shown that GABA treatment during development using GABA, nipecotic acid (a known GABA reuptake inhibitor) and creatinine (a potential activator of GABA_A receptor) rescued the lethality induced by glutamate toxicity of dFmr1 mutant flies, when they were reared on food containing increased levels of glutamate (Chang et al., 2008) and rescued many Fmr1 mutant phenotypes, such as *Futsch* overexpression, defects in mushroom bodies structure and altered male courtship behaviour (Chang et al., 2008). In addition, treatment of Fmr1 KO mice with the GABA_A receptor agonist taurine is reported to increase acquisition of a passive-avoidance task (El Idrissi et al., 2009). More recently, a treatment with the systemically active agonist acting at δ subunit-containing GABA_A receptors, 4,5,6,7-Tetrahydroisoxazolo[5,4-c]pyridin-3-ol hydrochloride (THIP hydrochloride), that is able to determine an augmentation of tonic inhibitory tone (Glykys & Mody, 2007), was shown to rescue neuronal hyperexcitability recorded from principal neurons of BL nucleus of amygdala in Fmr1 KO mice (Olmos-Serrano et al., 2010).

The involvement of GABA_B receptors is also under investigation in FXS. In fact, it has been observed a reduced expression of the GABA_B R1 subunits in the forebrain of Fmr1 KO mice, early during the development and in adulthood; whereas no significant differences have been observed in GABA_B R2 expression (Adusei et al., 2010; Pacey et al., 2011). Reduced functioning of GABA_B receptors might explain the increased susceptibility of Fmr1 KO mice to audiogenic seizures (Musumeci et al., 2000). Accordingly, stimulation of GABA_B receptors with agonist Baclofen reduces the rate of audiogenic seizures in Fmr1 KO mice (Pacey et al., 2009). These receptors play also a role in the pathophysiology of anxiety and depression, so GABA_B receptor agonist treatment might be used for reducing anxiety symptoms in patients with FXS (Cryan & Kaupmann, 2005).

3.4 Protein dysregulation and other biochemical pathways as potential targets of intervention

As soon as the list of validated FMRP-targeted mRNAs will grow, more pathways will be shown to be affected and more drugs will be proposed for the future therapy of FXS. In the next paragraph we will discuss recent advances concerning relevant pathways which may lead to treatment.

3.4.1 Oxidative stress and fragile X syndrome

Several evidences suggest a role of oxidative stress in FXS. FXS patients display an increase in adrenocortical activity and an altered hypothalamic–pituitary–adrenal (HPA) axis (Hessl et al., 2004); adrenal hormones have been involved in the induction of brain oxidative stress resulting in oxidation of molecules and depletion of antioxidants such as glutathione (Herman & Cullinan, 1997). In *Fmr1* null flies changes in the expression of proteins involved in redox reactions have been observed, suggesting a possible alteration in the oxidative balance (Y.Q. Zhang et al., 2005). In the brain of *Fmr1* KO mice higher levels of reactive oxygen species, nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase activation, lipid and protein oxidation have been found, suggesting that a moderate increase in the oxidative stress in the brain may play a role in the pathophysiology of FXS (el Bekay et al., 2007). In addition, microarray identification has revealed altered mRNA translational profiles in the absence of FMRP, involving proteins which participate in homeostasis of the antioxidant status such as glutathione transferase and SOD1 (M.R. Brown et al., 2001; Miyashiro et al., 2003). Recently, a reduction of protein levels of SOD1 has been found in *Fmr1* null cells and brain (Bechara et al., 2009), suggesting that in the absence of FMRP the increase in brain oxidative stress might be due to the altered SOD1 expression. A comprehensive profiling of the metabolome of the *Fmr1*-deficient brain has revealed an increase in lipid-oxidized species at early age (Davidovic et al., in press), further corroborating the hypothesis that oxidative stress is indeed involved in FXS pathophysiology.

The therapeutic implication of these findings is that anti-oxidant agents may be useful in the treatment of FXS and are supported by recent results obtained in *Fmr1* KO mice after treatment with alpha-tocopherol and melatonin (de Diego-Otero et al., 2009; Romero-Zerbo et al., 2009). Chronic pharmacological treatment with alpha-tocopherol reverses pathophysiological hallmarks including free radical overproduction, oxidative stress, macroorchidism, and also behaviour and learning deficits (de Diego-Otero et al., 2009). Chronic administration of melatonin protects the *Fmr1* KO mouse from the oxidative stress in brain and testis, reverses several behavioural and learning deficits, normalizes several abnormalities observed in the *Fmr1* KO mouse, including biochemical hallmarks, such as free radical production in macrophage cells and brain slices, as well as carbonyl content in proteins and lipid peroxidation (Romero-Zerbo et al., 2009). Additionally, it also normalizes reduced glutathione levels in the brain and testis of *Fmr1* KO mice. The treatment controls corticosterone plasma levels, locomotion (hyperactivity), anxiety responses and fear learning deficits.

3.4.2 Matrix metallo-proteinase 9 and minocycline

Another example of protein dysregulated in the mouse model of FXS and considered a valuable target of a pharmacological treatment is the matrix metallo-proteinase 9 (MMP-9). MMP-9 is an extracellular endopeptidase that cleaves extracellular matrix proteins that impact synaptogenesis and spine morphology (Ethell & Ethell, 2007). MMP-9 could affect dendritic spine morphology by cleaving components of the extracellular matrix and/or cell surface proteins that participate in synaptogenesis and dendritic spine maturation (Ethell & Ethell, 2007). It has been shown that MMP-9s are elevated in the hippocampus of *Fmr1* KO mice and may be partially responsible for the immature dendritic spine profile of

hippocampal neurons and for synaptic instability (Bilousova et al., 2006). A treatment with minocycline, a tetracycline analogue that can inhibit matrix MMP-9 and reduce inflammation in the CNS, promotes the formation of mature dendritic spines and reduces dendritic spine abnormalities respectively in WT and Fmr1 KO hippocampal neurons. Indeed, it has been shown that excessive MMP-9 activity disrupts mature dendritic spines in hippocampal neurons. The beneficial effects of this drug on dendritic spine morphology are also accompanied by changes in the behavioural performance of 3-weeks-old Fmr1 KO mice (Bilousova et al., 2009).

Clinical trials have been started for patients with FXS and an open-label trial has been recently completed to study the effects of minocycline in patients with FXS (Utari et al., 2010). The results show that minocycline provides significant functional benefits to FXS patients, it is well-tolerated, and both adolescents and adults with FXS can benefit from minocycline treatment.

3.4.3 Phosphoinositide 3-kinase and FXS

It has been hypothesized that FMRP controls protein synthesis-dependent regulation of synaptic morphology and function through regulation of PI3K signalling. PI3K regulates different pathways. Deficiency of FMRP results in excess activity of PI3K; loss of FMRP leads to excess mRNA translation and synaptic protein expression of p110beta, a catalytic subunit of PI3K and a putative FMRP-target mRNA (Miyashiro et al., 2003). FMRP regulates the synthesis and synaptic localization of p110beta. In WT, mGlu receptor activation induces p110beta translation, p110beta protein expression, and PI3K activity; in contrast, both p110beta protein synthesis and PI3K activity are elevated and insensitive to mGlu receptor stimulation in Fmr1 KO mice. Excess of PI3K activity in the absence of FMRP can occur independently of mGlu receptors (Gross et al., 2010). PI3K is a downstream signalling molecule of many cell surface receptors; aberrant regulation of p110beta could provide a molecular explanation for dysregulation of D1 dopamine receptors (Wang et al., 2008), of Gq-proteins (Volk et al., 2007), and of Ras (Hu et al., 2008) observed in Fmr1 KO mice. Dysregulated PI3K signalling may also underlie the synaptic impairments in FXS. In support of this hypothesis, it has been observed that a treatment with LY294002 (PI3K antagonist) in Fmr1 KO neurons can rescue the enhanced AMPA receptor internalization and the increased spine density (Gross et al., 2010). Targeting excessive PI3K activity might thus be another therapeutic strategy for FXS.

4. Conclusion and future direction

A deeper understanding of the function of FMRP and the molecular mechanisms underlying FXS using animal models has recently led to propose new therapeutic approaches, which will prove to be corrected in the next future as soon as several ongoing clinical trials will be completed. As a consequence of altered protein expression both at pre- and post-synaptic levels it is possible that several interconnected biochemical pathways are altered in FXS. It will be important to identify these cascades. System biology approaches and bioinformatic tools may help to identify the metabolic consequences of dysregulated biochemical cascades in FXS and in other neurological disorders associated with intellectual disability and autism. Given the high number of proteins and pathways which are likely to be dysregulated in FXS

it will be also very important to establish which of them are involved in determining structural changes during development and which are more involved in plasticity defects.

It is possible that different therapeutic interventions might be used during development and in adult patients.

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