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Invited review

BDNF in fragile X syndrome

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ABSTRACT

Fragile X syndrome (FXS) is a monogenic disorder that is caused by the absence of FMR1 protein (FMRP). FXS serves as an excellent model disorder for studies investigating disturbed molecular mechanisms and synapse function underlying cognitive impairment, autism, and behavioral disturbance. Abnormalities in dendritic spines and synaptic transmission in the brain of FXS individuals and mouse models for FXS indicate perturbations in the development, maintenance, and plasticity of neuronal network connectivity. However, numerous alterations are found during the early development in FXS, including abnormal differentiation of neural progenitors and impaired migration of newly born neurons. Several aspects of FMRP function are modulated by brain-derived neurotrophic factor (BDNF) signaling. Here, we review the evidence of the role for BDNF in the developing and adult FXS brain.

This article is part of the Special Issue entitled 'BDNF Regulation of Synaptic Structure, Function, and Plasticity'.

1. Fragile X syndrome

1.1. Introduction

Fragile X syndrome (FXS) is the leading cause of inherited intellectual disability and a well characterized form of autism spectrum disease with an incidence of approximately 1 in 4000 males and 1 in 8000 females (Santoro et al., 2012). Among a genetically heterogeneous group of neurodevelopmental disorders, the monogenic FXS has turned out to be an excellent model disorder for studies investigating disturbed molecular mechanisms and synapse function underlying cognitive impairment, autism, and behavioral disturbance. Defects in the development, maintenance, and plasticity of neuronal network connectivity are implicated in FXS. Abnormalities in the dendritic spines and synaptic transmission have been found in brain of FXS individuals and *Fragile X mental retardation 1* knockout (*Fmr1* KO) mice (see recent reviews Bhakar et al., 2012; Santoro et al., 2012), a mouse model that replicates many behavioral and structural features of the human FXS and serves as an excellent experimental model for this disorder (Bakker et al., 1994; Kooy et al., 1996). Recent evidence suggests that there are numerous abnormalities in the early development in FXS, including abnormal differentiation of neural progenitor cells (NPCs) and impaired migration of newly born neurons (Castrén et al., 2005; Tervonen et al., 2009; Callan and Zarnescu, 2011; Saffary and Zhigang, 2011; Sheridan et al., 2011; Castren, 2012). Studies showing that changes in synaptic signaling in FXS can be corrected with targeted therapies have led to clinical trials opening new treatment strategies for not only FXS, but also for other developmental disorders where disrupted network function has been implicated (Hagerman et al., 2009; Healy et al., 2011).

Brain-derived neurotrophic factor (BDNF) is involved in the regulation of diverse processes of normal neural circuit development and function (Park and Poo, 2012). Alterations in the expression of BDNF and its tropomyosin-related kinase B (TrkB) receptor (Huang and Reichardt, 2001) are associated with defects in learning and memory (Linnarsson et al., 1997; Minichiello et al., 1999). Given the central role of BDNF in neuronal plasticity, the

Abbreviations: aNPCs, adult neural progenitor cells; ADHD, attention deficit and/or hyperactive disorder; BDNF, Brain-derived neurotrophic factor; CYFIP1, FMRP-interacting protein; *FMR1* gene, fragile X mental retardation 1 gene; *Fmr1* KO, fragile X mental retardation 1 knockout; FMRP, FMR1 protein; FXS, Fragile X syndrome; FXTAS, tremor/ataxia syndrome; GABA, gamma-aminobutyric acid; gp1, group 1; mGluR, metabotropic glutamate receptor; IP, intermediate progenitor; LTD, long-term depression; LTP, long-term potentiation; MPEP, 2-methyl-6-(phenylethynyl)pyridine hydrochloride; NMDA, N-methyl-D-aspartate receptor; NPC, neural progenitor cells; RNAi, RNA interference; TrkB receptor, tropomyosin-related kinase B receptor.

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interaction of BDNF and TrkB with the processes underlying the FXS phenotype is possible. We will here review the evidence of the role for BDNF in the developing and adult FXS brain.

1.2. Clinical features of FXS

FXS is usually diagnosed in preschool children with a speech delay and behavioral problems (Boyle and Kaufmann, 2010). A characteristic physical appearance of FXS males often includes a long face with prominent ears and macro-orchidism. The FXS phenotype includes impaired learning and memory, communication difficulties, poor motor coordination, social anxiety, hyperactivity, and restricted repetitive and stereotyped patterns of behavior (Chonchaiya et al., 2009). In addition, FXS individuals show abnormal responses to sensory stimuli (Miller et al., 1999; Castrén et al., 2003) and they often display self-injurious behavior such as self-biting (Symons et al., 2010). About 75% of FXS males meet the criteria for attention deficit and/or hyperactive disorder (ADHD) (Baumgardner et al., 1995) and 30% for autism with a distinct behavioral pattern (Hagerman et al., 2010; Wolff et al., 2012). Epileptic seizures are seen in 13–44% of FXS individuals (Berry-Kravis, 2002). Epilepsy in FXS shows an age-related appearance in the childhood or young adulthood. The seizures frequently involve temporal and frontal lobes. In brain imaging studies, consistent findings are enlarged caudate nuclei and reduced size of the amygdala and cerebellar vermis in brains of individuals with FXS (Reiss et al., 1995; Lightbody and Reiss, 2009).

1.3. Genetic basis of FXS

FXS is caused by a mutation in the *FMR1* gene on the X chromosome which leads to the functional loss of FMR1 protein (FMRP) (Verkerk et al., 1991). In most FXS individuals, a CGG trinucleotide repeat expansion with more than 200 repeats in the 5′end of the gene results in the methylation and transcriptional silencing of the gene (Wang et al., 2012a). In the general population, the CGG repeat number is in a range of 5–54 repeats and stable when transmitted to the next generation. Repeat lengths varying from 50 to 200 repeats are fragile X premutations which may become unstable through maternal transmission and increase in size in subsequent generations (Fu et al., 1991). The prevalence of the premutation has been estimated to be up to 1:100–300 in females. Female premutation carriers do not show deficits in their cognitive abilities but mild emotional involvement is seen in ~20% of carriers. A tremor/ataxia syndrome (FXTAS) with Parkinsonian features and dementia is described in premutation carriers at older ages with a higher penetrance in males than in females (Hagerman and Hagerman, 2004).

The methylation status of the mutation in the *FMR1* gene correlates with the severity of the cognitive deficits (Kaufmann et al., 1999). *Fmr1* KO mice replicate many features of FXS, including learning deficits, macro-orchidism, and susceptibility to epilepsy (Bakker et al., 1994; Spencer et al., 2011).

1.4. The FMR1 protein (FMRP)

FMRP is a RNA-binding protein that is highly expressed in the normal central nervous system and testes (Devys et al., 1993). FMRP interacts directly or through adapter molecules with a number of transcripts, including many mRNAs encoding proteins involved in neuronal and synapse function (Zalfa et al., 2003; Darnell et al., 2011; Ascano et al., 2012). As a constituent of messenger ribonucleoprotein complexes, FMRP controls protein translation in various subcellular sites (Khandjian et al., 1996; Feng et al., 1997; Stefani et al., 2004; Tatavarty et al., 2012) and regulates mRNA localization (Dictenberg et al., 2008) and stability (Zalfa et al., 2007) (Fig. 1). The nuclear localization signal allows FMRP dimers to enter the nucleus where FMRP interacts with specific mRNAs and proteins. This messenger ribonucleoprotein complex is then exported out of the nucleus by the nuclear export signal of FMRP. The absence of FMRP increases translation indicating that FMRP normally represses translation (Bhakar et al., 2012). FMRP can inhibit translation by stalling the ribosomes during the elongation or by interacting with the cytoplasmic complex of FMRP-interacting

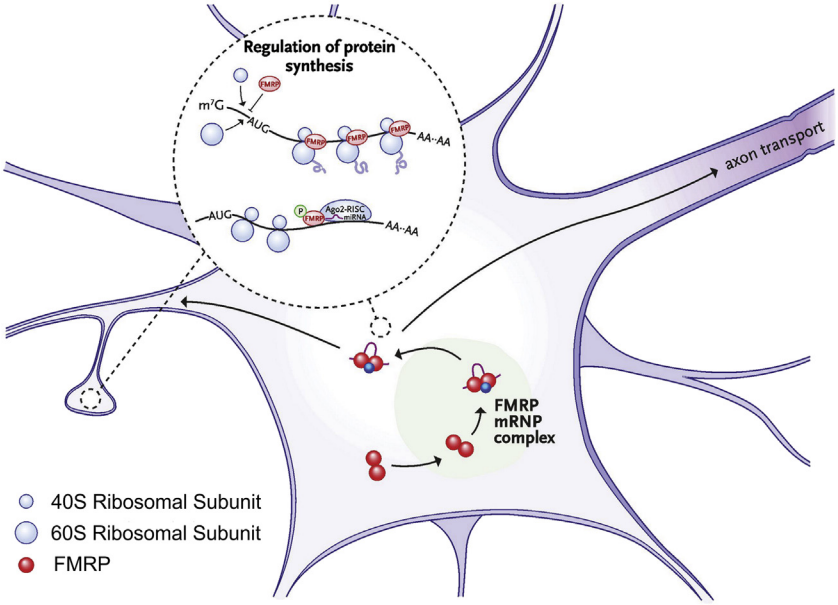

Fig. 1. FMRP function in the neuron. FMRP dimerizes in the cytoplasm and enters nucleus where FMRP interacts with specific mRNAs and proteins to form a messenger ribonucleoprotein (mRNP) complex. FMRP is part of an RNA-protein complex in cytoplasm and the majority of cytoplasmic FMRP is associated with polyribosomes. FMRP regulates the subcellular localization, stability, and local translation of mRNAs. FMRP may repress translation by stalling the elongation of actively translating ribosomes and by blocking the initiation of ribosome assembly. The absence of FMRP and the inhibitory associations result in increased protein synthesis in FXS. FMRP interacts with miRNAs and members of the RISC complex in the FMRP–RISC ribonucleoprotein (FMRP–RISC–RNP) complex. The miRNAs facilitate the selection and repression of target mRNAs by FMRP.