Decreased fragile X mental retardation protein (FMRP) is associated with lower IQ and earlier illness onset in patients with schizophrenia

Tamás Kovács a, Oguz Kelemen b, Szabolcs Kéri a,c,*

a National Psychiatry Center, Budapest, Hungary
b Bács-Kiskun County Hospital, Psychiatry Center, Kecskemét, Hungary
c University of Szeged, Faculty of Medicine, Department of Physiology, Szeged, Hungary

ARTICLE INFO

Article history:
Received 19 November 2011
Received in revised form 28 September 2012
Accepted 20 December 2012

Keywords:
Schizophrenia
Fragile X syndrome
IQ
Neurodevelopment

ABSTRACT

The purpose of this study was to investigate Fragile X Syndrome (FXS)-related mechanisms in schizophrenia, including CGG triplet expansion, FMR1 mRNA, and fragile X mental retardation protein (FMRP) levels in lymphocytes. We investigated 36 patients with schizophrenia and 30 healthy controls using Southern blot analysis, mRNA assay, and enzyme-linked immunosorbent assay (ELISA). General intellectual functions were assessed with the Wechsler Adult Intelligence Scale-III, and the clinical symptoms were evaluated with the Positive and Negative Syndrome Scale. Results revealed that, relative to healthy controls, CGG triplet size and FMR1 mRNA were unaltered in patients with schizophrenia. However, the FMRP level was significantly reduced in patients compared with controls. We found an association between lower FMRP levels, reduced IQ, and earlier illness onset in schizophrenia. Chlorpromazine-equivalent antipsychotic dose did not correlate with FMRP levels. These results raise the possibility of impaired translation of FMR1 mRNA, altered epigenetic regulation, or increased degradation of FMRP in schizophrenia, which may play a role in dysfunctional neurodevelopmental processes and impaired neuroplasticity.

1. Introduction

Fragile X mental retardation protein (FMRP) is an RNA binding protein, which is abundant in the soma and dendritic spines of neurons. FMRP is a translational suppressor for several genes encoding proteins critical for synaptic transmission and plasticity, such as subunits of glutamate receptors and postsynaptic proteins (O’Donnell and Warren, 2002; Bear et al., 2008; Rousseau et al., 2011). The absence of FMRP characterizes fragile X syndrome (FXS), which is a prevalent form of inherited mental disabilities (Reiss and Hall, 2007). In FXS, the absence of FMRP is due to the silencing of the FMR1 gene, which is caused by the expansion of a CGG trinucleotide repeat (Xq27.3, >200 repeats in the full syndrome; 55–200 repeats in premutation carriers) and increased methylation of the promoter region (O’Donnell and Warren, 2002; Bear et al., 2008; Rousseau et al., 2011).

There is increasing evidence that FMR1/FMRP is also involved in the pathogenesis of other disorders, such as premature ovarian insufficiency, fragile X-associated tremor/ataxia syndrome, and autism (Hagerman et al., 2010). Moreover, the spectrum of fragile X-related disorders might include some forms of schizophrenia, anxiety, and mood disorders (Bourgeois et al., 2009; Fatemi and Folsom, 2011). This hypothesis was recently supported by the observation of Fatemi et al. (2010), who described reduced FMRP expression in the lateral cerebellum of patients with schizophrenia, bipolar disorder, and major depressive disorder. FMRP is implicated in glutamatergic and GABA-ergic processes, which are key pathophysiological mechanisms of schizophrenia (Fatemi and Folsom, 2011).

The purpose of the present study was to investigate whether FMRP is decreased in the peripheral blood of patients with schizophrenia and to assess its relationship with FMR1 mRNA level. In addition, we explored the relationship between FMRP expression and clinical characteristics of the patients. We hypothesized that FMRP is associated with IQ, given that the absence of this protein is accompanied by a severe cognitive disability in patients with FXS.

2. Methods

2.1. Participants

Participants comprised 36 outpatients with schizophrenia and 30 healthy volunteers. The control participants were university/hospital employees and their non-biological relatives and acquaintances. All participants were assessed with...
were converted into chlorpromazine equivalents (Woods, 2003). The patients did not receive any other psychotropic medications at the time of testing (olanzapine: $n = 11$, quetiapine: $n = 4$, risperidone plus quetiapine: $n = 7$). Antipsychotic doses were converted into chlorpromazine equivalents (Woods, 2003). The patients did not receive any other psychotropic medications at the time of testing. Table 1 summarizes the results. Given that the variables were not normally distributed, as revealed by Kolmogorov–Smirnov tests, we used non-parametric Mann–Whitney U-tests. Patients with schizophrenia displayed normal CGG triplet size and $FMR1$ mRNA level. In contrast, the level of FMRP was significantly altered in patients with schizophrenia. An alternative explanation is that the degradation of FMRP is accelerated in schizophrenia. Future studies should also take into consideration the potential role of epigenetic regulations of $FMR1$ (Stöger et al., 2011).

The most important finding of the study was that decreased FMRP was associated with earlier illness onset and lower IQ. This suggests that reduced FMRP may be related to neurodevelopmental changes, neuroplasticity, and cognitive functions. An extensive meta-analysis of thousands of cases and controls, it was confirmed that greater premorbid IQ decrement is associated with earlier illness onset (Khandaker et al., 2011). In the case of cross-sectional studies, however, neuropsychological functions are linked to current IQ instead of to IQ trajectory during the disease course (Kremen et al., 2008).

Similarly to our previous study (Kéri and Benedek, 2011, 2012), we found no significant correlation between IQ and FMRP in patients with schizophrenia. This similar tendency may suggest that FMRP may be implicated in neurodevelopment and neuroplasticity underlying the emergence of general cognitive abilities, and it is not disease specific for schizophrenia. Previously, we observed similar correlations between visual functions and FMRP expression in healthy controls (Kéri and Benedek, 2011, 2012), with a special reference to contrast sensitivity functions disrupted in FXS and schizophrenia (Slaghuis, 1998; Kogan et al., 2004). In this case, similarly to IQ, FMRP may be important, even under non-pathological circumstances, in the physiological range of expression.

Loat et al. (2006) studied the relationship between $FMR1$ allele length and cognitive functions in low ability, control, and high-IQ children. In males, there was a significant negative correlation...
دریافت فوری
متن کامل مقاله
امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات