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A role for synapsin in FKBP51 modulation of stress responsiveness: Convergent evidence from animal and human studies

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Summary Both the molecular co-chaperone FKBP51 and the presynaptic vesicle protein synapsin (alternatively spliced from *SYN1—3*) are intensively discussed players in the still insufficiently explored pathobiology of psychiatric disorders such as major depression, schizophrenia and posttraumatic stress disorder (PTSD). To address their still unknown interaction, we compared the expression levels of synapsin and five other neurostructural and HPA axis related marker proteins in the prefrontal cortex (PFC) and the hippocampus of restrained-stressed and unstressed *Fkbp5* knockout mice and corresponding wild-type littermates. In addition, we compared and correlated the gene expression levels of *SYN1*, *SYN2* and *FKBP5* in three different online datasets comprising expression data of human healthy subjects as well as of predominantly medicated patients with different psychiatric disorders. In summary, we found that *Fkbp5* deletion, which we previously demonstrated to improve stress-coping behavior in mice, prevents the stress-induced decline in prefrontal cortical (pc), but not in hippocampal synapsin expression. Accordingly, pc, but not hippocampal, synapsin protein levels correlated positively with a more active mouse stress coping behavior. Searching for an underlying mechanism, we found evidence that deletion of *Fkbp5* might prevent stress-induced pc synapsin loss,

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at least in part, through improvement of pc Akt kinase activity. These results, together with our finding that *FKBP5* and *SYN1* mRNA levels were regulated in opposite directions in the PFC of schizophrenic patients, who are known for exhibiting an altered stress-coping behavior, provide the first evidence of a role for pc synapsin in FKBP51 modulation of stress responsiveness. This role might extend to other tissues, as we found *FKBP5* and *SYN1* levels to correlate inversely not only in human PFC samples but also in other expression sites. The main limitation of this study is the small number of individuals included in the correlation analyses. Future studies will have to verify the here-postulated role of the FKBP51—Akt kinase—synapsin pathway in stress responsiveness.

1. Introduction

The molecular co-chaperone and hypothalamic—pituitary—adrenal (HPA) axis regulator FK506 binding protein 51 (FKBP51) is one of the most vividly discussed drug-targets and biomarkers in major depression (MDD) and posttraumatic stress disorder (PTSD) to date, mostly because distinct alleles of the *FKBP5* gene were found to be associated with these two highly prevalent psychiatric disorders (Binder, 2009; Schmidt et al., 2013b, 2014). Some of these *FKBP5* risk alleles were reported to be linked to enhanced cortisol-inducibility of *FKBP5* mRNA as well as to higher *FKBP5* expression in human peripheral blood monocytes (PBMC) (Binder, 2008; O'Leary et al., 2011), thereby suggesting elevated *FKBP5* expression as a potential pathogenetic factor for affective disorders (Binder, 2009; O'Leary et al., 2011). As a study reporting on *FKBP5* expression in schizophrenic patients found an increase in pc *FKBP5* mRNA levels in patients with schizophrenia (SCZ) vs. healthy controls (HC) (Sinclair et al., 2013), elevated *FKBP5* expression levels might possibly represent a pathogenetic factor also for SCZ. In contrast, in PTSD patients vs. HC, one study found relatively *decreased* (Yehuda et al., 2009), another *unaltered* (Neylan et al., 2011) peripheral *FKBP5* mRNA levels.

FKBP51 and other tetratricopeptide repeat (TPR) proteins like the closely related FKBP52 protein compete for binding to the major heat shock protein (hsp) 90 which is required for GR cortisol binding in vivo (Kirschke et al., 2014). Hsp90 belongs to the complex cascade of molecular chaperones (heterocomplex) that catalyzes the conformational changes enabling the GR and other steroid receptors (SR) to translocate into the nucleus (mature complex) where they exert their genomic functions (Supplemental Fig. 1, for review see, for example, Galigniana et al., 2012; Storer et al., 2011). Binding of the co-chaperone FKBP51 to hsp90 antagonizes FKBP52 effects and results inter alia in SR inhibition (Galigniana et al., 2012; Schülke et al., 2010). GCs like cortisol regulate the activity of the HPA axis through negative feedback via the GR and the mineralocorticoid receptor (MR) (Galigniana et al., 2012).

Besides FKBP51, the presynaptic vesicle protein synapsin is another important candidate molecule in psychiatric disorders: synapsin expression was shown to be reduced in both the hippocampus and the PFC of schizophrenic patients as well as in the hippocampus of bipolar disorder (BD) patients vs. HC (Tan et al., 2013; Vawter et al., 2002). The synapsin family, which controls neurotransmitter release (Cesca et al., 2010; Medrihan et al., 2013), comprises 10 homologous proteins: synapsin Ia—b, synapsin IIa—b, and synapsin IIIa—f; these isoforms are generated by alternative splicing of three genes, i.e. *SYN1*, *SYN2*, *SYN3* (Cesca et al., 2010). Polymorphisms in *SYN2* were reported to be associated with SCZ (Cesca et al., 2010). Synaptic loss in conjunction with a decrease in expression of synapse-related genes like *SYN1* was found in postmortem PFC samples of MDD patients (Kang et al., 2012). Accordingly, another study found the expression of pc *SYN1* and *SYN2* to be reduced in MDD but, interestingly, to be elevated in BD patients (Cruceanu et al., 2012). We found no clinical study on synapsin expression in PTSD patients. However, recently, we demonstrated a long-lasting reduction in hippocampal presynaptic proteins, including synapsin, in mice suffering from a PTSD-like syndrome (Herrmann et al., 2012). In summary, both FKBP51 and synapsin are obviously major players in the pathobiology of various psychiatric disorders. To improve the comprehensibility of the complex literature on FKBP51 and synapsin expression in mental diseases, we summarized the major findings of the respective studies cited here in Supplemental Table 1.

The stress responsiveness of FKBP51 and synapsin appears to be their most obvious functional similarity: the expression of both molecules can be modulated by glucocorticoids (GC) and by various types of stressors: GC-treatment of cultured cells was reported to increase both *FKBP5* mRNA levels (Tissing et al., 2007) and synapsin Ia/Ib levels (Revest et al., 2010a). In accordance, GC-treatment of MDD patients vs. HC also resulted in an increase in whole blood *FKBP5* mRNA expression in both groups, however, MDD was associated with a relatively lower induction of *FKBP5* (Menke et al., 2012). The majority of animal studies report a stress-induced elevation in cerebral *Fkbp5* mRNA expression levels — mainly in the regions of the hippocampus, the PFC and the amygdala (Guidotti et al., 2013; Scharf et al., 2011; Wagner et al., 2012). In contrast, one study that analyzed FKBP51 *protein* expression found a *reduction* in FKBP51 levels in the PFC of prenatally stressed rats (Szymańska et al., 2009). A reduction in *synapsin* protein levels was inter alia observed in the hippocampus of our mouse model of PTSD (Herrmann et al., 2012) and of prenatally stressed rats (Marrocco et al., 2012), while elevated synapsin levels were found in the hypothalamus and the nucleus accumbens of chronically stressed rats (Bessa et al., 2013; Ge et al., 2013). Interestingly, in rodent studies, antidepressant-mediated relief