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Fkbp52 heterozygosity alters behavioral, endocrine and neurogenetic parameters under basal and chronic stress conditions in mice

Jakob Hartmann*, Klaus V. Wagner, Nina Dedic, Daria Marinescu, Sebastian H. Scharf, Xiao-Dong Wang, Jan M. Deussing, Felix Hausch, Theo Rein, Ulrike Schmidt, Florian Holsboer, Marianne B. Müller, Mathias V. Schmidt

Max Planck Institute of Psychiatry, Kraepelinstr. 2-10, 80804 Munich, Germany

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Summary Aversive life events represent one of the main risk factors for the development of many psychiatric diseases, but the interplay between environmental factors and genetic predispositions is still poorly understood. One major finding in many depressed patients is an impaired regulation of the hypothalamic—pituitary—adrenal (HPA) axis. The negative feedback loop of the HPA axis is mediated via the glucocorticoid receptor (GR) and the mineralocorticoid receptor. The co-chaperones FK506-binding protein 51 (FKBP51) and FK506-binding protein 52 (FKBP52) are components of the heat shock protein 90-receptor-heterocomplex and are functionally divergent regulators of both receptors. Here, we characterized heterozygous Fkbp52 knockout ($Fkbp52^{+/-}$) mice under basal or chronic social defeat stress (CSDS) conditions with regard to physiological, neuroendocrine, behavioral and mRNA expression alterations. $Fkbp52^{+/-}$ mice displayed symptoms of increased stress sensitivity in a subset of behavioral and neuroendocrine parameters. These included increased anxiety-related behavior in the elevated plus-maze and an enhanced neuroendocrine response to a forced swim test (FST), possibly mediated by reduced GR sensitivity. At the same time, $Fkbp52^{+/-}$ mice also demonstrated signs of stress resilience in other behavioral and neuroendocrine aspects, such as reduced basal corticosterone levels and more active stress-coping behavior in the FST following CSDS. These contrasting results are in line with previous reports showing that FKBP52 is not involved in all branches of GR signaling, but rather acts in a gene-specific manner to regulate GR transcriptional activation.

* Corresponding author. Tel.: +49 089 30622 233; fax: +49 089 30622 610.
E-mail address: jhartmann@mpipsykl.mpg.de (J. Hartmann).

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1. Introduction

Susceptibility to psychiatric disorders such as major depression is determined by the relationship between genetic predisposition and environmental factors including negative life events and chronic stress (Hammen, 2005; El Hage et al., 2009; Gillespie et al., 2009; Hyde et al., 2011). However, the molecular mechanisms underlying individual vulnerability or resilience to chronic stress are still poorly understood.

The hypothalamus–pituitary–adrenal (HPA) axis represents one of the major stress-systems in mammals, which ultimately leads to the release of glucocorticoids (GCs) from the adrenal cortex. GCs are then acting on numerous organ systems, including the brain, to modulate metabolism and behavior. In parallel, GCs activate a negative feedback circuit via glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) at different levels of the HPA axis, thereby terminating the stress response (de Kloet et al., 1998; Ulrich-Lai and Herman, 2009).

GRs and MRs are ligand-dependent transcription factors (de Kloet and Reul, 1987). The process of receptor folding, maturation, activation, trafficking and subsequent receptor action on gene transcription is regulated by a multiprotein complex that assembles around the molecular chaperone heat shock protein 90 (hsp90) (Pratt et al., 2006; Grad and Picard, 2007). The FK506-binding protein 51 (FKBP51, encoded by the FKBP5 gene) and FK506-binding protein 52 (FKBP52, encoded by the FKBP4 gene) are components of the chaperone-receptor heterocomplex and differentially regulate the GR or MR at two levels: hormone binding and nuclear translocation. FKBP51 has been shown to decrease ligand binding sensitivity of the receptor and efficiency of nuclear translocation (Denny et al., 2000; Scammell et al., 2001; Wochnik et al., 2005; Westberry et al., 2006). Upon ligand binding, FKBP51 is replaced by FKBP52, which in turn binds to dynein. This promotes the translocation of the receptor-complex into the nucleus and enhances subsequent DNA-binding (Davies et al., 2002; Wochnik et al., 2005; Gallo et al., 2007; Galigniana et al., 2010; Schülke et al., 2010). For a detailed illustration and description of the mechanism see review of Binder (2009).

In numerous clinical studies, single nucleotide polymorphisms of FKBP51 have repeatedly been associated with stress-related diseases such as posttraumatic stress disorder and major depression (Yehuda et al., 2009; Zobel et al., 2010; Zou et al., 2010; Mehta et al., 2011). In addition, we could recently show that Fkbp51 knockout (51KO) mice were less affected by chronic social defeat stress (CSDS), in a subset of neuroendocrine and behavioral parameters (Hartmann et al., 2012). Furthermore, 51KO mice displayed enhanced active stress coping behavior following an acute severe stress exposure which was independently also shown in aged 51KO mice, likely due to a more sensitive GR (O'Leary et al., 2011; Touma et al., 2011).

In contrast, most studies with Fkbp52 knockout ($Fkbp52^{-/-}$) mice focused on developmental and molecular aspects. In this regard it is important to know that $Fkbp52^{-/-}$ mice show an increased embryonic lethality, while the Mendelian ratio of heterozygous Fkbp52 ($Fkbp52^{+/-}$) mice is normal (Cheung-Flynn et al., 2005; Tranguch et al., 2005; Warrier et al., 2010). Nonetheless, several studies revealed an androgen, progesterone, and glucocorticoid insensitivity in $Fkbp52^{-/-}$ mice (Cheung-Flynn et al., 2005; Tranguch et al., 2005; Yang et al., 2006; Yong et al., 2007; Warrier et al., 2010). Furthermore, it has been shown that female $Fkbp52^{-/-}$ mice are infertile as a result of embryonic implantation and decidualization failure caused by uterine defects and progesterone insensitivity (Tranguch et al., 2005, 2007; Yang et al., 2006). Male $Fkbp52^{-/-}$ mice display several defects in reproductive tissues such as ambiguous external genitalia and dysgenic prostate consistent with partial androgen insensitivity (Cheung-Flynn et al., 2005; Yong et al., 2007). In addition, $Fkbp52^{+/-}$ mice showed a susceptibility to high-fat diet induced hepatic steatosis, due to a state of glucocorticoid resistance arising from liver-specific loss of GR activity (Warrier et al., 2010).

All these findings suggest that FKBP52 plays an important role in steroid receptor function. However, a comprehensive behavioral, endocrine and neurogenetic characterization combined with challenging conditions such as chronic stress is still lacking. To fill this gap, we investigated the function of FKBP52 and its potential role in the development of stress-related disorders. We characterized heterozygous Fkbp52 knockout mice under basal and chronic stress conditions. Mice were then analyzed for alterations in physiological, neuroendocrine, behavioral and mRNA expression parameters. We hypothesized that $Fkbp52^{+/-}$ mice would display a higher stress sensitivity due to a partial glucocorticoid insensitivity.

2. Materials and methods

2.1. Animals and housing conditions

The Fkbp52 knockout mouse line was previously generated as described by Cheung-Flynn et al. (2005) and were kept on a mixed 129SvJ × C57BL/6 background. Due to the low viability of null embryos, we used $Fkbp52^{+/-}$ mice in this study, obtained from heterozygous breeding pairs. Genotypes were verified by PCR of tail DNA. Only male mice were used for the experiment. Animals were 12 weeks old at the start of the experiment. Mice were singly housed two weeks prior to the experiment. Maintenance and experiments were performed under a 12 h light, 12 h dark cycle (lights on at 0800 h) and constant temperature (23 ± 2 °C) conditions. Food and water were provided ad libitum.

Male CD1 mice (12–16 weeks old) serving as residents were allowed to habituate to the social defeat cage for two weeks before the onset of the experiments. Male juvenile Balb/c mice (5 weeks old) serving as social targets in the sociability test were housed in groups of 4. The experiments were performed in accordance with the European Communities Council Directive 2010/63/EU. All efforts were made to minimize animal suffering during the experiments. The protocols were approved by the committee for the Care and Use of Laboratory Animals of the Government of Upper Bavaria, Germany.

2.2. Chronic social defeat paradigm

The CSDS paradigm was conducted as described previously (Wagner et al., 2011; Wang et al., 2011; Hartmann et al., 2012). Briefly, the experimental mice were introduced into