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The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress

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ABSTRACT

Chronic stress is increasingly considered to be a main risk factor for the development of a variety of psychiatric diseases such as depression. This is further supported by an impaired negative feedback of the hypothalamic-pituitary-adrenal (HPA) axis, which has been observed in the majority of depressed patients. The effects of glucocorticoids, the main hormonal endpoint of the HPA axis, are mediated via the glucocorticoid receptor (GR) and the mineralocorticoid receptor. The FK506-binding protein 51 (FKBP5), a co-chaperone of the Hsp90 and component of the chaperone-receptor heterocomplex, has been shown to reduce ligand sensitivity of the GR. This study aimed to investigate the function of FKBP5 as a possible mediator of the stress response system and its potential role in the development of stress-related diseases. Therefore, we assessed whether mice lacking the gene encoding FKBP5 (51KO mice) were less vulnerable to the adverse effects of three weeks of chronic social defeat stress. Mice were subsequently analyzed with regards to physiological, neuroendocrine, behavioral and mRNA expression alterations. Our results show a less vulnerable phenotype of 51KO mice with respect to physiological and neuroendocrine parameters compared to wild-type animals. 51KO mice demonstrated lower adrenal weights and basal corticosterone levels, a diminished response to a novel acute stimulus and an enhanced recovery, as well as more active stress-coping behavior. These results suggest an enhanced negative glucocorticoid feedback within the HPA axis of 51KO mice, possibly modulated by an increased sensitivity of the GR.

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1. Introduction

In daily life, humans are repeatedly exposed to periods of stress. The short-term effects of stress are mostly beneficial by promoting adaptation, as long as the stress response is efficiently shut off. In contrast, excessive challenges like chronic stress clearly impose a major risk factor for the development of a variety of psychiatric diseases such as anxiety-related disorders and depression (de Kloet et al., 2005a; McEwen, 2004).

The major control module of the stress response in mammals, besides the autonomic nervous system, is the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoids (GCs), which are the main hormonal endpoint of the HPA axis, regulate the activity of the HPA axis through negative feedback via the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). MRs and GRs mediate this regulation mainly in the hypothalamus and the pituitary, but also on the level of the hippocampus and other limbic structures (De Kloet et al., 1998; Ulrich-Lai and Herman, 2009). The proper negative feedback via the GR is critical for a healthy stress response. One of the most robust biological abnormalities observed in the majority of depressed patients is altered signaling via the GR, which often leads to an impaired negative feedback regulation and thus to partial glucocorticoid resistance (Holsboer, 2000; Pariante and Miller, 2001).

The GR is a member of the ligand-dependent transcription factor family (De Kloet and Reul, 1987). Upon ligand binding, the receptor

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undergoes a conformational change, translocates from the cytosol to the nucleus and modulates gene transcription. The process of GR activation, trafficking and subsequent GR action on gene transcription is regulated by a multiprotein complex that assembles around the molecular chaperone heatshock protein 90 (hsp90) (Pratt et al., 2006). The hsp90 complex is crucial for proper folding, maturation, translocation and DNA binding of the GR and consists of numerous co-chaperones (Grad and Picard, 2007). These include, among others, the immunophilins FK506-binding protein 51 (FKBP5) and FK506-binding protein 52 (FKBP4). Recent studies have shown that FKBP5 is a key player of the GR-hsp90 complex. Once FKBP5 is bound to the GR complex via hsp90, the receptor's affinity for cortisol is decreased (Riggs et al., 2003; Wochnik et al., 2005). Upon ligand binding, FKBP5 is replaced by FKBP4, which in turn binds to dynein. This promotes the translocation of the GR complex into the nucleus and subsequent DNA binding (Binder, 2009; Davies et al., 2002; Wochnik et al., 2005). In neurons, siRNA knockdown of the gene encoding FKBP5 is associated with elevated baseline GR nuclear translocation (Tatro et al., 2009). The endogenous overexpression of FKBP5 in squirrel monkeys has been demonstrated to be causative for their glucocorticoid resistance (Denny et al., 2000; Scammell et al., 2001; Westberry et al., 2006). Moreover, the expression of FKBP5 is stimulated by steroids, such as GCs, as part of an intracellular ultra-short negative feedback loop for GR activity (Hubler and Scammell, 2004; Vermeer et al., 2003). Therefore, augmented transcription and translation of FKBP5 following corticoid receptor activation reduces GR sensitivity. In addition, FKBP5 mRNA expression has recently been shown to be increased in brain regions such as the hippocampus, central amygdala and PVN of mice, after a single dexamethasone treatment (Scharf et al., 2011).

The suggested role of FKBP5 in GR signal transduction may represent a new possibility to elucidate GR impairment associated with many psychiatric disorders such as depression (Holsboer, 2000). It is well established that malfunction of GRs due to low affinity ligand binding can be the consequence of mutations of the receptor itself or of limited hsp90 action (Bohen and Yamamoto, 1993; Brönnegard et al., 1996; Picard et al., 1990). In humans, genetic variations of FKBP5 have been associated with a major risk factor for the development of posttraumatic stress disorder (PTSD) (Binder et al., 2008; Segman et al., 2005; Yehuda et al., 2009). Furthermore, the same alleles have been linked with the regulation of the HPA axis in depression, with an enhanced recurrence of depressive episodes, and with a faster antidepressant treatment response. In addition, these polymorphisms predispose individuals to increased sensitivity to psychosocial stress (Binder et al., 2004; Ising et al., 2008; Kirchheiner et al., 2008; Lekman et al., 2008). Specifically, it has been shown that the risk alleles result in a higher FKBP5 expression, thereby lowering GR sensitivity, which is suggested to be the underlying mechanisms for the increased sensitivity to psychosocial stress.

It is still largely unclear why some individuals are more susceptible to develop a stress-related disorder, while others turn out to be resilient. Recent studies suggest that genetic predispositions interact with environmental demands such as chronic stress (Binder, 2009; Gillespie et al., 2009; Pezawas et al., 2005; Schmidt et al., 2010). However, the molecular mechanisms underlying individual susceptibility or resilience to chronic stress are still poorly understood. Given the fact that FKBP5 has been suggested to be a possible mediator of the stress response system and its potential role in the development of stress-related disorders, we hypothesised that mice lacking the FKBP5 gene may show a lower vulnerability to chronic stress exposure. To test this hypothesis, we analyzed the response of conventional FKBP5 knockout (51KO) mice to a chronic social defeat stress (CSDS) paradigm at the behavioral, neuroendocrine and molecular level.

2. Methods

2.1. Animals and housing conditions

The FKBP5 knockout mouse line (51KO) was previously generated (Tranguch et al., 2005). Since *fkbp5* is too large to efficiently target all coding sequences, a *lacZ*/neomycin cassette was inserted in place of sequences from exons 1–2. The partially disrupted gene retains the endogenous FKBP5 promoter and expresses β-galactosidase in-frame with the FKBP5 initiation codon (Supplemental Fig. 1A). Details of the generation of the 51KO mice are provided in the Supplemental material. Genotypes were verified by PCR and Southern analysis of tail DNA, and the absence of FKBP51 protein was verified by fluorescence immunohistochemistry and western blotting of mouse tissue extracts (Supplemental Fig. 1B and C). Since most of the *fkbp5* exons were retained and could potentially encode a truncated protein in transgenic mice, Westerns were repeated with four anti-FKBP5 monoclonal antibodies having distinct epitopes and with a rabbit polyclonal antibody prepared against full-length FKBP5; none of these antibodies detected an FKBP5 protein product (results not shown). 51KO mice did not show overt reproductive failures and no abnormalities in the survival rate. The genotypes of the offspring corresponded approximately to the Mendelian ratios and sex was equally distributed. Only male mice were used for the experiment, obtained from heterozygous breeding pairs. Animals were 13 weeks old at the start of the experiment. Mice were singly housed as adults at least two weeks prior to the experiment. Maintenance and experiments were performed under a 12 h light, 12 h dark cycle (lights on at 7:00 am) and constant temperature (23 ± 2 °C) conditions. Food and water were provided *ad libitum*.

Male CD1 mice (19–21 weeks old) serving as residents were held under the same conditions as described above and were allowed to habituate to the social defeat cage for two weeks before the onset of the experiments. The experiments were performed in accordance with European Communities Council Directive 86/609/EEC. 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 stress paradigm

The CSDS paradigm was performed as described previously (Wagner et al., 2011). In short, mice were subjected to daily bouts of social defeat by a resident mouse, which was physically superior and specifically trained for aggressive behavior towards intruders. The animals were separated as soon as the aggressive confrontation was accomplished, or after a maximum of 5 min. Subsequently, the animals spent 24 h in the same cage (45 cm × 25 cm), which was divided by a mesh partition, to prevent physical, but allow sensory contact. Every day, stressed animals were introduced to a new resident cage, in order to exclude a repeated encounter with the same resident throughout the experiment. Experimental mice were always defeated by resident males during the course of the experiment. Control mice were held in their home cages for the entire experimental period. All mice were handled daily; fur status and weight were determined every 3–4 days before social defeat was enforced.

The condition of fur was assessed by an experienced investigator as described previously (Mineur et al., 2003). In short, scores were classified according to a 4-point scale, where 1 stands for a perfect, clean fur, while 4 represents a disheveled, scruffy fur, often including traces of wounds and scurf. Ratings of 2 and 3 demonstrate intermediate fur states, respectively.

2.3. Experimental design

Initially, 24 wild-type (WT) and 21 51KO mice were split into four groups ($n = 13$ WT control, $n = 11$ 51KO control, $n = 11$ WT stress and $n = 10$ 51KO stress) and subjected to the CSDS paradigm for 21 days. The daily defeat occurred between 12:00 pm and 4:00 pm; varying starting times limited the predictability of the stressor and therefore minimized a potential habituation effect. During the third week of the procedure, all behavioral tests were performed.

2.4. Behavioral analysis

Behavioral tests were carried out between 08:00 am and 12:00 pm in the same room where the animals were housed. All tests were performed using an automated video-tracking system (Anymaze 4.20, Stoelting, IL, USA).

2.4.1. Open-field test

The open-field (OF) test was conducted on day 15 of the CSDS paradigm. Testing was performed in an empty open-field arena (50 cm × 50 cm × 50 cm) made of gray polyvinyl chloride (PVC), which was evenly illuminated with 15 lux. Testing duration was 15 min, divided into three segments of 5 min each. Parameters of interest included the total distance traveled and the time of immobility.

2.4.2. Elevated plus-maze

On day 16 of the stress procedure, the elevated plus-maze (EPM) test was performed. The apparatus consisted of a plus-shaped platform with two opposing open

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