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Forebrain glucocorticoid receptor gene deletion attenuates behavioral changes and antidepressant responsiveness during chronic stress

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ABSTRACT

Stress is an important risk factor for mood disorders. Stress also stimulates the secretion of glucocorticoids, which have been found to influence mood. To determine the role of forebrain glucocorticoid receptors (GR) in behavioral responses to chronic stress, the present experiments compared behavioral effects of repeated social defeat in mice with forebrain GR deletion and in floxed GR littermate controls. Repeated defeat produced alterations in forced swim and tail suspension immobility in floxed GR mice that did not occur in mice with forebrain GR deletion. Defeat-induced changes in immobility in floxed GR mice were prevented by chronic antidepressant treatment, indicating that these behaviors were dysphoria-related. In contrast, although mice with forebrain GR deletion exhibited antidepressant-induced decreases in tail suspension immobility in the absence of stress, this response did not occur in mice with forebrain GR deletion after defeat. There were no marked differences in plasma corticosterone between genotypes, suggesting that behavioral differences depended on forebrain GR rather than on abnormal glucocorticoid secretion. Defeat-induced gene expression of the neuronal activity marker c-fos in the ventral hippocampus, paraventricular thalamus and lateral septum correlated with genotype-related differences in behavioral effects of defeat, whereas c-fos induction in the nucleus accumbens and central and basolateral amygdala correlated with genotype-related differences in behavioral responses to antidepressant treatment. The dependence of both negative (dysphoria-related) and positive (antidepressant-induced) behaviors on forebrain GR is consistent with the contradictory effects of glucocorticoids on mood, and implicates these or other forebrain regions in these effects.

Abbreviations: AM, morning; BLA, basolateral amygdale; CamKIIα-Cre, Transgene expressing Cre recombinase under control of the calcium calmodulin kinase IIα promoter; CeA, central amygdale; Cort, corticosterone; FBGRKO-T29-1, Mice with forebrain glucocorticoid receptor deletion derived on a pure C57BL/6 strain from a commercial founder transgenic for calcium calmodulin kinase IIα-Cre (see Methods); GR, glucocorticoid receptor(s); HPA, hypothalamic–pituitary–adrenocortical; LS, lateral septum; MR, mineralocorticoid receptor(s); NAc, nucleus accumbens; PVN, paraventricular hypothalamus; pvThal, paraventricular thalamus; vHPC, ventral hippocampus; ilPFC, infralimbic prefrontal cortex

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1. Introduction

A variety of studies have found that stress increases the risk of clinically significant emotional disorders (Caspi et al., 2003; Jacobs et al., 1990; Maes et al., 2000). The mechanisms underlying the psychiatric risks of stress are largely undefined, although they have been linked, for example, to interaction with genetic factors such as serotonin transporter isoforms (Caspi et al., 2003). However, genetic make-up is difficult to modify, indicating a need to explore other mechanisms by which stress can influence mental health.

Stress is also a major stimulus for glucocorticoid secretion by the hypothalamic–pituitary–adrenocortical (HPA) axis. Glucocorticoids have been found to have a variety of negative effects on mood ranging from anxiety and depression to psychosis, even in individuals lacking a family or personal history of psychiatric disease. Such effects have been correlated with elevated glucocorticoid levels in Cushing's syndrome and in patients receiving glucocorticoids for immunologic disorders (Brown, 2009; Kenna et al., 2011). Glucocorticoids are also often elevated in depression, a finding that has been attributed to deficits in glucocorticoid receptors responsible for HPA feedback inhibition (Ising et al., 2007). Although the significance of the increase in glucocorticoids remains a matter of debate, there is limited but intriguing evidence to suggest that glucocorticoids can contribute to depression symptoms (Rakofsky et al., 2009; Wolkowitz et al., 2009). Consistent with the clinical literature, glucocorticoids have also been shown to have depression- and anxiety-like effects in rodents (Mitchell and Meaney, 1991; Sterner and Kalynchuk, 2010; Tronche et al., 1999; Veldhuis et al., 1985; Wei et al., 2004). However, glucocorticoids have also been found to have mood-elevating effects (Brown 2009; Kenna et al., 2011), and depression has also been suggested to be due to deficits in glucocorticoids receptors mediating positive mood (Sudheimer et al., 2013). Glucocorticoids are therefore a logical and compelling connection between stress and affective disease risk.

Glucocorticoids can bind in brain to either the higher-affinity mineralocorticoid receptor (MR) or the lower affinity glucocorticoid receptor (GR). GR is widely expressed throughout the brain and thought to mediate the effects of elevated levels of glucocorticoids, whereas MR is concentrated in but not limited to limbic structures (Jacobson, 2005) and thought to be more sensitive to low glucocorticoid levels (Jacobson, 2005). Although there is some evidence that MR can affect emotion-related behavior in rodents (Lai et al., 2007; Mostalac-Preciado et al., 2011; Rozeboom et al., 2007; Smythe et al., 1997; Wu et al., 2013), depression- and anxiety-like symptoms are most frequently evoked in humans and animals at elevated levels of glucocorticoids (Brown, 2009; Kenna et al., 2011; Schelling et al., 2006), which are more likely to activate GR. Therefore, GR are the most plausible candidate to be involved in the mood effects of glucocorticoids.

GR in a variety of forebrain regions have been implicated in affective dysfunction (Boyle et al., 2005; Calfa et al., 2007; Kolber et al., 2008; Korte et al., 1996; McKlveen et al., 2013; Sudheimer et al., 2013; Yang et al., 2006). Mice with forebrain GR deletion have been created by transgenic expression of Cre recombinase under control of the calcium calmodulin kinase IIα (CamKIIα) promoter in floxed GR mice. The original model of forebrain GR deletion, derived on a mixed-strain background from the T50 founder line of the CamKIIα-Cre transgene, was reported to have a depression-like phenotype, consisting of increased depression-like behavior and elevated HPA activity relative to that in floxed GR mice (Boyle et al., 2005). However, this depression-like phenotype was not found in mice with forebrain GR deletion derived on a pure C57BL/6 background from the T29-1 founder line of the CamKIIα-Cre transgene, even though forebrain GR deletion was at least as extensive (Vincent et al., 2013). The latter mouse model, hereafter referred to as FBGRKO-T29-1 (Vincent et al., 2013), offers a convenient model to test the role of forebrain GR in the behavioral effects of chronic stress, without potential confounds from baseline differences in HPA activity or depression-like behavior. The current experiments compared the effects of repeated social defeat stress or control cage exposures, with and without antidepressant treatment, on depression-related behavior in FBGRKO-T29-1 mice and their genetic controls, floxed GR mice. Although chronic stress elicited changes in behavior in floxed GR mice that were opposite to those conventionally interpreted as correlates of depression, these changes were associated with social aversion, a depression-like behavior (Krishnan et al., 2007), and were reversed by chronic antidepressant treatment, suggesting that behavioral alterations were dysphoria-related. FBGRKO-T29-1 mice failed to exhibit these stress-related changes in behavior and were resistant to the effects of antidepressant treatment during chronic stress, suggesting GR involvement in both negative (dysphoria-related) and positive (antidepressant-induced) effects on mood.

2. Results

2.1. *Experiment 1: effects of forebrain GR deletion on behavioral and HPA responses to repeated social defeat*

Social interaction with a novel conspecific has been used as a measure of depression-like behavior, with lower levels of interaction interpreted as greater depression-like behavior (Krishnan et al., 2007). Interaction with a novel mouse exhibited a significant main effect of defeat ($F_{1,34}=8.852$; $P=0.0054$) but no significant main effects of genotype or genotype x defeat interaction. Defeated floxed GR mice exhibited significantly less time investigating the novel mouse than did control floxed GR mice (Table 1). There was a similar trend for defeated FBGRKO-T29-1 mice to exhibit less interaction with a novel mouse, but

Table 1 – Results of the social interaction test in floxed GR and FBGRKO-T29-1mice on day 15 of control cage exposures (Control) or repeated social defeat (Defeat) from Experiment 1. Data are time (sec) mice spent interacting with a novel CD-1 male mouse that was confined in a perforated plastic box.

Floxed GR		FBGRKO-T29-1	
Control	Defeat	Control	Defeat
59±15 N=8	24±4* N=11	66±19 N=8	35±7 N=11

* $P<0.05$ vs. control in the same genotype.