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Role of corticosteroid binding globulin in emotional reactivity sex differences in mice

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Summary Sex differences exist for stress reactivity as well as for the prevalence of depression, which is more frequent in women of reproductive age and often precipitated by stressful events. In animals, the differential effect of stress on male's and female's emotional behavior has been well documented. Crosstalk between the gonadal and stress hormones, in particular between estrogens and glucocorticoids, underlie these sex differences on stress vulnerability.

We have previously shown that corticosteroid binding globulin (CBG) deficiency in a mouse model (Cbg k.o.) leads, in males, to an increased despair-like behavior caused by suboptimal corticosterone stress response. Because CBG displays a sexual dimorphism and is regulated by estrogens, we have now investigated whether it plays a role in the sex differences observed for emotional reactivity in mice.

By analyzing Cbg k.o. and wild-type (WT) animals of both sexes, we detected sex differences in despair-like behavior in WT mice but not in Cbg k.o. animals. We showed through ovariectomy and estradiol (E2) replacement that E2 levels explain the sex differences found in WT animals. However, the manipulation of E2 levels did not affect the emotional behavior of Cbg k.o. females. As Cbg k.o. males, Cbg k.o. females have markedly reduced corticosterone levels across the circadian cycle and also after stress. Plasma free corticosterone levels in Cbg k.o. mice measured immediately after stress were blunted in both sexes compared to WT mice. A trend for higher mean levels of ACTH in Cbg k.o. mice was found for both sexes. The turnover of a corticosterone bolus was increased in Cbg k.o. Finally, the glucocorticoid-regulated immediate early gene early growth response 1 (*Egr1*) showed a blunted mRNA expression in the hippocampus of Cbg k.o. mutants while mineralocorticoid and glucocorticoid receptors presented sex differences but equivalent mRNA expression between genotypes.

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Thus, in our experimental conditions, sex differences for despair-like behavior in WT mice are explained by estrogens levels. Also, in both sexes, the presence of CBG is required to attain optimal glucocorticoid concentrations and normal emotional reactivity, although in females this is apparent only under low E2 concentrations. These findings suggest a complex interaction of CBG and E2 on emotional reactivity in females.

1. Introduction

Women and men present differential risks for the occurrence and symptomatology of stress-induced depression, with women of reproductive age being around two times as likely as men to report a lifetime history of a major depressive episode (Kessler et al., 1993; Wittchen et al., 2011). While social factors certainly contribute to these differences, biological sex differences are also known to play an important role (Schotte et al., 2006).

Fluctuations in estrogen levels, rather than their absolute levels, have been shown to be an important risk factor for the onset of depressive symptoms in women. Accordingly, depressive episodes appear more frequently during the premenstrual, postpartum and perimenopausal periods (Solomon and Herman, 2009; Young and Korszun, 2010). Preclinical models have confirmed the importance of female sex hormones in affecting emotions and cognition (ter Horst et al., 2012).

Physiologic stress responses, in particular hypothalamic-pituitary-adrenal (HPA) axis reactivity culminating in glucocorticoid release, are also believed to underlie the sex differences in the prevalence of depression. This endocrine system is dysregulated in a significant number of depressive patients and its activity/reactivity displays a sexual dimorphism. Depressed patients generally present a hyperactivity of the HPA axis, i.e. increased circulating cortisol levels, often explained by an impaired feedback regulation and leading to excessive glucocorticoid signaling in the brain (Pariante and Lightman, 2008; Young and Korszun, 2010). Although much less studied, hypoactivity of the HPA axis, leading to low or inefficient cortisol levels, is also observed in some types of depression (Bremmer et al., 2007; Gold and Chrousos, 2002; Raison and Miller, 2003).

Sex differences in HPA axis regulation are well documented in animal (Handa et al., 1994; Rhodes and Rubin, 1999) as well as in human studies (Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005). Both basal and stimulated HPA axis activities are generally increased in female when compared to male rodents (Rhodes and Rubin, 1999). In human studies, reported sex differences in HPA axis response to stress are inconsistent, as they appear to be influenced by age, type of stressors, phase of the menstrual cycle, or oral contraceptive intake (Kudielka et al., 2009; Young and Korszun, 2010).

Prime candidates for explaining such sex differences in HPA axis activity are circulating gonadal steroids levels, with endogenous estradiol (E2) being known to increase (except during pregnancy) and testosterone to decrease both ACTH and cortisol (corticosterone in rodents) responses to stress (Handa et al., 1994; Seale et al., 2004, 2005; Solomon and Herman, 2009). E2 has been shown to increase central HPA axis drive in rodents through its stimulating effects on corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) mRNA expression, as well as by increasing adrenal sensitivity to ACTH (Solomon and Herman, 2009). Additionally, estrogens are thought to increase glucocorticoids levels indirectly by positively stimulating corticosteroid binding globulin (CBG) synthesis, as observed during pregnancy (Moore et al., 1978), after the intake of oral contraceptives containing ethinylestradiol (Qureshi et al., 2007; White et al., 2006) or in vitro through a mechanism involving the estrogen receptor alpha (Nader et al., 2006). Hormonal replacement studies have provided conflicting findings about the effects of exogenous E2 on HPA axis response to acute stress (Solomon and Herman, 2009; Young and Korszun, 2010). In most cases, the administration of physiological doses of E2 decreases ACTH and/or corticosterone responses to acute stressors, whereas supraphysiological doses increase these hormones on gonadectomized animals (Solomon and Herman, 2009).

CBG or transcortin is a glycoprotein binding glucocorticoids with high-affinity in vertebrate blood. CBG plays an essential role in glucocorticoid availability and delivery to target tissues (Gagliardi et al., 2010; Moisan, 2010). In our previous studies, we showed that CBG deficiency in male mice led to an insufficient glucocorticoid signaling and delivery to the brain, associated with altered stress-induced emotional and cognitive behaviors. Indeed, we showed that during stress these mutant mice display a lower rise of glucocorticoids than the wild-type (WT) controls, associated with altered emotional reactivity in the forced swim, tail suspension and learned helplessness tests. These data suggested that CBG plays a role in the fast actions of glucocorticoids on behavior. We then demonstrated that stress-induced memory retrieval impairment, an example of the fast action of glucocorticoids on the brain, is abolished in the Cbg k.o. mice. This effect of stress on memory retrieval was restored in the Cbg k.o. mice by infusing corticosterone directly into the hippocampus. The mechanisms explaining these effects involved an increased clearance but no difference in corticosterone production (Minni et al., 2012; Moisan et al., 2014; Richard et al., 2010).

Considering CBG role in glucocorticoid-dependent emotional behavior in male mice, as well as the importance of estrogens in CBG regulation, the present study aimed at determining the influence of CBG deficiency on emotional behaviors displayed by female mice and its role in the sex differences already described for these behaviors. We first examined emotional behavior in WT and Cbg k.o. mice, then we studied the role of estrogens in the behavior of females from both genotypes and finally we