Psychoneuroendocrinology (2006) 31, 692–702

PNEC

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Hypoestrogenism does not mediate social suppression of cortisol in subordinate female marmosets

Wendy Saltzman[a,b,c,*], Brynn K. Hogan[c], Amy J. Allen[c], Brian M. Horman[c], David H. Abbott[c,d]

[a]Department of Biology, University of California, Riverside, CA 92521, USA
[b]Neuroscience Graduate Program, University of California, Riverside, CA, USA
[c]National Primate Research Center, University of Wisconsin, Madison, WI, USA
[d]Department of Obstetrics and Gynecology, University of Wisconsin, Madison, WI, USA

Received 12 August 2005; received in revised form 20 January 2006; accepted 26 January 2006

KEYWORDS
Marmoset;
Reproductive suppression;
Subordination;
Ovariectomy;
Adrenal cortex;
Cortisol

Summary Behaviorally subordinate female marmosets undergo social suppression of ovulation and hypoestrogenism, as well as chronic reductions in circulating basal cortisol concentrations. Because estrogen elevates hypothalamic–pituitary–adrenal axis activity and circulating glucocorticoid levels in other species, we tested the hypothesis that socially induced hypoestrogenism contributes to cortisol reductions in subordinate female marmosets. We characterized morning basal plasma cortisol levels, as well as cortisol responses to exogenous adrenocorticotropic hormone (ACTH; 0, 1, or 10 μg/kg), in seven anovulatory subordinate females and six ovariectomized, non-subordinate females under two conditions: during long-term treatment with estradiol (E_2) and control. Circulating E_2 and cortisol levels were compared to those of six dominant females undergoing ovulatory cycles. Basal cortisol concentrations in the control condition were significantly lower in subordinates than in both dominant and ovariectomized females. E_2 treatment elevated circulating E_2 levels of subordinate and ovariectomized females into the range seen in dominant females but did not increase either mean basal or ACTH-stimulated cortisol levels. To the contrary, E_2 treatment caused a decline in basal cortisol levels over time, especially in ovariectomized animals. These results indicate that treatment with exogenous estrogen does not elevate circulating cortisol levels in previously hypoestrogenemic female marmosets and, correspondingly that socially induced hypoestrogenism does not diminish cortisol levels in subordinate females.
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1. Introduction

Behaviorally subordinate individuals in many species exhibit altered activity of the stress-responsive hypothalamic–pituitary–adrenal (HPA) axis as

* Corresponding author. Tel.: +1 951 827 6356; fax: +1 951 827 4286.
E-mail address: saltzman@ucr.edu (W. Saltzman).

0306-4530/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2006.01.006

compared to dominants. Traditionally, subordinates have been thought to manifest elevated HPA activity and, consequently, increased circulating glucocorticoid concentrations as a result of psychosocial stress (von Holst, 1998; Blanchard et al., 2002). More recently, however, it has become evident that subordinates may frequently manifest *reduced* circulating or excreted glucocorticoid concentrations as compared to dominant individuals (Saltzman et al., 1994, 1998; Creel, 2001; Goymann and Wingfield, 2004). Several authors have suggested that subordinate individuals in these societies experience less psychosocial stress or lower allostatic load than dominants (Creel et al., 1996; Creel, 2001; Abbott et al., 2003; Goymann and Wingfield, 2004). In addition, we (Saltzman et al., 1994, 1998, 2000) have suggested that low glucocorticoid levels in subordinate animals may be mediated in part by low levels of reproductive hormones, especially in species in which subordinate individuals undergo social suppression of reproduction. A number of reproductive hormones, including estrogen, progesterone, androgens, luteinizing hormone (LH) and chorionic gonadotropin (CG), have been shown to modulate HPA activity (e.g. Phillips and Poolsanguan, 1978; Kime et al., 1980; O'Connell et al., 1994; Young, 1995, 1998). Socially induced suppression of these hormones in subordinate individuals may therefore be expected to contribute to rank-related differences in glucocorticoid levels.

We have been investigating the interactions between reproductive and adrenocortical activity in the common marmoset (*Callithrix jacchus*), a small, New World monkey in which endocrine function is profoundly influenced by social status. Social groups in both the wild and captivity may contain as many as six adult females, but only one or two behaviorally dominant females breed in each group (reviewed by French, 1997; Saltzman, 2003). Subordinate females are often anovulatory and hypoestrogenemic as a result of inadequate secretion of CG (Abbott et al., 1981, 1988; Saltzman et al., 1998), the major luteinizing gonadotropin secreted by the pituitary in this species and possibly other New World primates (Gromoll et al., 2003; Müller et al., 2004). This socially induced infertility can persist for months or even years, but is reversed rapidly following separation of the subordinate female from her dominant female groupmate (Abbott et al., 1988; Abbott and George, 1991).

Anovulatory subordinate female marmosets also undergo chronic suppression of circulating cortisol levels (Saltzman et al., 1994, 1998, 2004; Johnson et al., 1996; Abbott et al., 1997). Morning basal cortisol levels decline dramatically within 6–7 weeks following the onset of social subordination and anovulation (Saltzman et al., 1994, 1998; Abbott et al., 1997) and can remain suppressed for months to years (Saltzman et al., 1998; unpublished data). Dominant and subordinate females have not been found to differ in morning basal adrenocorticotropin (ACTH) levels or in suppression of ACTH or cortisol by dexamethasone (DEX), a synthetic glucocorticoid (Saltzman et al., 2004). Following suppression of endogenous ACTH and cortisol by DEX, however, subordinates exhibited blunted cortisol responses to exogenous ACTH as compared to dominant females (Saltzman et al., 2000). Moreover, cortisol responses to ACTH were virtually identical in ovary-intact subordinates and ovariectomized, non-subordinate females, indicating that this adrenocortical impairment might be mediated by withdrawal of ovarian hormones rather than by social subordination per se (Saltzman et al., 2000). Consistent with this possibility, basal plasma cortisol concentrations fluctuate reliably across the ovarian cycle in marmosets, showing a midcycle peak during the late follicular, ovulatory, and early luteal phases and a decline across the luteal phase (Saltzman et al., 1998). Thus, circulating cortisol levels may be modulated by reproductive hormones in female marmosets.

These previous findings suggest that cortisol diminution in subordinate female marmosets is effected by two mechanisms: (1) reduced adrenal responsiveness to ACTH, which in turn may be mediated by suppression of ovarian hormones, and (2) an additional inhibitory mechanism, presumably triggered directly by social subordination and acting at the level of the brain or pituitary, which restrains ACTH secretion in spite of the reduced negative-feedback signal from low cortisol levels and reduces basal cortisol levels of subordinates below those of ovariectomized females (Saltzman et al., 1998). In view of the well-known stimulatory effects of estrogen on HPA activity (reviewed by Kime et al., 1980; Young, 1995, 1998; Wilson et al., 2005), we hypothesize that the first of these mechanisms, adrenal hyporesponsiveness, may be mediated by hypoestrogenism. In this study, we tested this hypothesis by determining the effects of long-term estradiol treatment on basal cortisol levels and cortisol responses to exogenous ACTH in both ovariectomized females and anovulatory, socially subordinate females.

2. Methods

2.1. Animals

We used 19 captive-born, adult female common marmosets (*Callithrix jacchus*), including six

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