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Social suppression of cortisol in female marmosets: Role of luteinizing hormone/chorionic gonadotropin

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Abstract

Behaviorally subordinate female common marmosets (*Callithrix jacchus*) undergo suppression of ovulation and chronic reductions in basal plasma cortisol concentrations. Indirect evidence suggests that hypophyseal chorionic gonadotropin (CG; the major pituitary luteinizing gonadotropin in marmosets) may elevate cortisol concentrations in female marmosets, and therefore that social suppression of CG may contribute to diminution of cortisol in subordinates. To test this hypothesis, we determined whether pharmacological inhibition of pituitary CG release decreases basal and adrenocorticotropin (ACTH)-stimulated cortisol secretion. We characterized cortisol and reproductive hormone concentrations in six ovary-intact and six ovariectomized marmosets during long-term treatment with leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist, and vehicle. Leuprolide suppressed basal plasma CG concentrations, abolished the CG response to exogenous GnRH, and, in intact animals, blocked ovarian cyclicity. During treatment with vehicle, plasma cortisol concentrations were elevated during the periovulatory phase in intact females, compared to the follicular phase, the luteal phase, and ovariectomized females. Leuprolide suppressed basal cortisol concentrations of intact females as compared to the periovulatory phase, but did not affect basal cortisol in ovariectomized animals and did not alter responses to exogenous ACTH. These findings suggest that elevations in circulating CG concentrations are associated with elevated cortisol concentrations in female marmosets, and that this relationship requires simultaneous increases in ovarian hormones that occur only during the periovulatory period. Thus, suppression of CG release in anovulatory subordinate females may not play an important role in socially induced diminution of cortisol.

Keywords: Adrenal cortex; *Callithrix jacchus*; Chorionic gonadotropin; Cortisol; Leuprolide acetate; Luteinizing hormone; Marmoset; Ovarian cycle; Ovariectomy; Subordination

1. Introduction

Complex, bidirectional interactions occur between the female reproductive system and the hypothalamic–pituitary–adrenal (HPA) axis. While much attention has been focused on the role of the stress-responsive HPA axis in suppressing female reproductive function, it is also well established that hormones of the hypothalamic–pituitary–ovarian axis can modulate HPA activity (reviewed by Kime et al., 1980; Young, 1998). Estrogen, in particular, is well known to stimulate HPA activity and elevate circulating glucocorticoid concentrations in rodents and primates through actions on the hypothalamus, pituitary, adrenal, and liver. Progesterone may modulate these effects of estrogen and may also interfere with binding of glucocorticoids to their receptors and to corticosteroid-binding globulin, thereby altering glucocorticoid negative-feedback effects. HPA activity may also be modulated by the pituitary gonadotropin luteinizing hormone (LH) and the structurally and functionally homologous placental hormone, chorionic gonadotropin (CG). Although these effects have received much less attention than those

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of the gonadal steroids, evidence from several species suggests that LH/CG can elevate circulating glucocorticoid concentrations through direct actions on the adrenal cortex (Kero et al., 2000; O'Connell et al., 1994; Pabon et al., 1996; Phillips and Poolsanguan, 1978; Vinson and Renfree, 1975; Vinson et al., 1976).

We have been investigating the interactions between reproductive hormones and the HPA axis in the common marmoset (*Callithrix jacchus*), a small New World monkey in which endocrine function is profoundly influenced by social status. Social groups may contain as many as six adult females, but in both the wild and captivity, 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 inhibited hypophyseal secretion of CG (Abbott et al., 1981a,b; Saltzman et al., 1998), which has been shown recently to be the major luteinizing gonadotropin secreted by the pituitary in this species and possibly other New World primates (Gromoll et al., 2003; Müller et al., 2004b). Reproductive suppression can persist for months or even years, but is reversed rapidly following separation of the subordinate female from her dominant female groupmate (Abbott and George, 1991; Abbott et al., 1988).

Anovulatory, subordinate female marmosets also exhibit chronic reductions in circulating cortisol concentrations. Morning basal (i.e., non-stressed) cortisol concentrations decline markedly within 6–7 weeks following the onset of social subordination and anovulation, and can remain low for months to years (Abbott et al., 1997; Johnson et al., 1996; Saltzman et al., 1994, 1998, 2004b, in press, 2006). Diminished cortisol concentrations are associated with reduced adrenal responsiveness to adrenocorticotropic hormone (ACTH): subordinate females have basal plasma ACTH concentrations that are similar to those of dominants (Johnson et al., 1996; Saltzman et al., 2004b, in press), and therefore have reliably lower cortisol-to-ACTH ratios (Saltzman et al., in press). Moreover, subordinates secrete less cortisol than dominants in response to exogenous ACTH (Saltzman et al., 2000). Subordinate females also exhibit elevated ACTH concentrations following treatment with metyrapone, an inhibitor of cortisol biosynthesis, as compared to dominant females, indicative of altered central regulation of the HPA axis (Saltzman et al., in press).

Cortisol diminution in subordinate female marmosets appears to be mediated, in part, by suppression of reproductive hormones. For example, pair-housed females that are anovulatory but not subordinate to other females exhibit low plasma cortisol concentrations and do not show a further reduction in cortisol upon becoming subordinate in a new social group (Saltzman et al., 1994). Moreover, basal cortisol concentrations fluctuate reliably across the ovarian cycle in marmosets, indicating that HPA activity is modulated by reproductive hormones (Saltzman et al., 1998). In a recent study (Saltzman et al., 2006), however, we found that long-term pharmacologic elevation of circulating estradiol concentrations into the range typical of the periovulatory phase of the ovarian cycle did not appreciably elevate basal or ACTH-stimulated cortisol concentrations in either anovulatory subordinates or ovariectomized, non-subordinate females. Hypoestrogenism, therefore, does not appear to contribute to cortisol suppression in subordinates.

In contrast, indirect evidence suggests that hypophyseal CG may elevate circulating cortisol concentrations in female marmosets, and therefore that suppression of CG release in subordinates may contribute to cortisol diminution. First, in females undergoing ovulatory cycles, morning basal plasma cortisol concentrations peak during the periovulatory period, when CG secretion is maximal (Saltzman et al., 1998). Moreover, basal cortisol concentrations of cycling females are reliably higher than those of ovariectomized marmosets only during the periovulatory period, when CG concentrations of cycling females exceed those of ovariectomized females (Saltzman et al., 1998). Subordinates, in contrast, have consistently lower circulating concentrations of both cortisol and CG than ovariectomized females (Saltzman et al., 1998, 2006). Finally, in one study, morning basal plasma cortisol

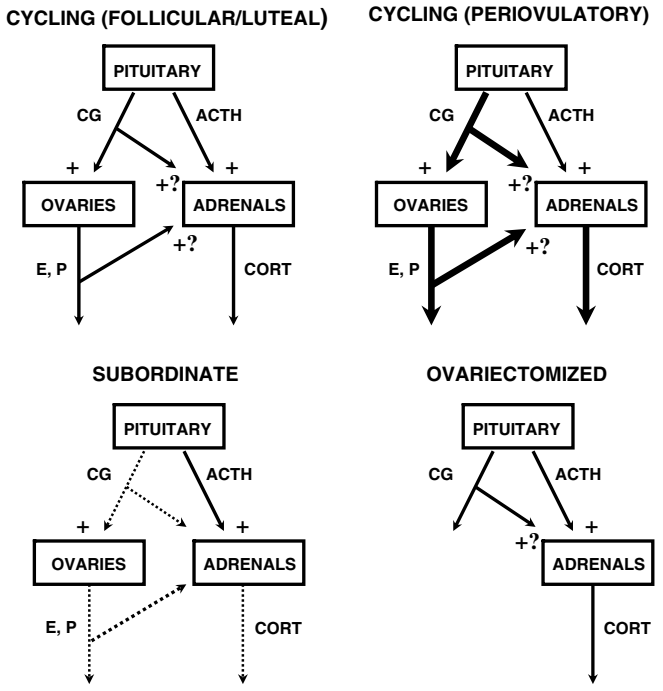

Fig. 1. Hypothesized interactions among hypophyseal chorionic gonadotropin (CG), ovarian steroids (estrogen [E] and progesterone [P]), and cortisol secretion in female marmosets. Anovulatory subordinates have consistently low circulating concentrations of CG and cortisol, but not ACTH, as compared to both cycling and ovx females, as well as low, acyclic concentrations of E and P. Cycling females exhibit elevated CG and cortisol during the periovulatory phase, the only time when both hormones are reliably elevated above those in ovx females. Thus, CG is hypothesized to enhance basal cortisol secretion in cycling and ovx females, as compared to subordinate females, and to further elevate cortisol secretion during the ovulatory phase of the ovarian cycle. This latter effect may be dependent upon the ovarian steroid milieu around the time of ovulation. Thickness of arrow indicates relative hormone concentrations.