Effect of stress-like concentrations of cortisol on the feedback potency of oestradiol in orchidectomized sheep

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Abstract

The effect of stress-like concentrations of cortisol on oestradiol-induced change in LH secretion and GnRH receptor expression was evaluated in orchidectomized sheep (wethers). Twenty-four wethers were assigned at random to one of the four treatment groups in a 2x2 factorial design (n = 6 wethers/group). Wethers received cortisol (90 μg/kg/h; groups 2 and 4) or a comparable volume of cortisol delivery vehicle (groups 1 and 3) by continuous infusion for 48 h. During the final 24 h of infusion, wethers received oestradiol (6 ng/kg/h; groups 3 and 4) or oestradiol delivery vehicle (groups 1 and 2). The pattern of LH secretion was assessed during a 3-h period of intensive blood collection beginning 21 h after initiation of oestradiol infusion. Although neither cortisol nor oestradiol alone affected (P > 0.05) mean serum concentration of LH or LH pulse frequency, serum LH and the frequency of secretory episodes of LH were significantly reduced (P < 0.05) in wethers receiving cortisol and oestradiol in combination. Anterior pituitary tissue was collected at the end of the infusion period. Oestradiol increased (P < 0.05) tissue concentrations of GnRH receptor and GnRH receptor mRNA. Although cortisol alone did not affect (P > 0.05) basal concentrations of receptor or receptor mRNA, the magnitude of oestradiol-induced increase in GnRH receptor and GnRH receptor mRNA was significantly reduced in wethers receiving cortisol and oestradiol concurrently. Conversely, steady-state concentrations of mRNA encoding the LHβ and FSHβ subunits were increased (P < 0.05) in wethers receiving cortisol. These observations demonstrate that stress-like concentrations of cortisol act in concert with oestradiol to suppress LH secretion. In addition, cortisol blocks oestradiol-dependent...
increase in pituitary tissue concentrations of GnRH receptor and GnRH receptor mRNA. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Cortisol; Sheep; Oestradiol; Gonadotropin secretion; GnRH receptor mRNA

1. Introduction

Marked and persistent increase in the serum concentration of glucocorticoids is a component of the endocrine response to many physical or psychological stressors in primates (Chen et al., 1992; Norman et al., 1994), rodents (Cook et al., 1973; Suzuki et al., 1986), and domestic species (Caraty et al., 1990; Guillaume et al., 1992; Komesaroff and Funder, 1994). This increase in glucocorticoids may be causally linked to the inhibition of reproductive function that is another physiological correlate that often accompanies stress. Indeed, extended administration of natural or synthetic glucocorticoids has an anti-gonadal effect in rodents (Smith et al., 1971; Baldwin and Sawyer, 1974), primates (Cunningham et al., 1978; Hayashi and Moberg, 1990) and sheep (Daley et al., 1999a).

The anti-gonadal effect of stress and/or glucocorticoids is due, at least in part, to the decrease in gonadotropin secretion that occurs during stress (Chen et al., 1992; Norman et al., 1994) or prolonged administration of glucocorticoids (Fonda et al., 1984; Dubey and Plant, 1985). This stress- or glucocorticoid-dependent reduction in gonadotropin secretion may be the consequence of reduced hypothalamic activity and/or decreased pituitary sensitivity. Interestingly, the reduction in gonadotropin secretion induced by stress (Chen et al., 1992) or exogenous glucocorticoid (Vreeburg et al., 1984, 1988) is accentuated by gonadal steroids. Indeed, Vreeburg et al. have suggested that glucocorticoids enhance the negative feedback potency of gonadal steroids. This postulate is consistent with our recent observation that the negative feedback response to oestradiol in sheep is amplified after chronic administration of cortisol (Daley et al., 1999b).

In the work presented, we extend our earlier studies by examining the feedback response to oestradiol in castrated male sheep after short-term exposure to stress-like concentrations of cortisol. Continuous infusion of cortisol was used to establish a stable serum concentration of cortisol that approximated the serum concentration noted in sheep during exposure to potent stressors, such as bacterial endotoxin or profound hypoglycemia (Coleman et al., 1993; Komesaroff and Funder, 1994; Battaglia et al., 1997). Oestrogenic effects were assessed in sheep receiving exogenous oestradiol at a rate sufficient to establish serum concentrations of oestradiol of 2–3 pg/ml. During the breeding season, this concentration of oestradiol does not affect the mean serum concentration of LH or the episodic character of LH secretion in unstressed wethers (Sakurai et al., 1995). However, this level of oestradiol does induce a marked increase in the concentration of GnRH receptor and GnRH receptor mRNA in pituitary tissue of male sheep (Sakurai et al., 1995; Adams et al., 1996). We hypothesized that short-term exposure to stress-like concentrations of cortisol would increase the feedback effect of oestradiol on LH secretion and reduce oestrogen-dependent increase in pituitary concentrations of GnRH receptor and GnRH receptor mRNA.
2. Materials and methods

2.1. Animals

Spring-born crossbred Suffolk lambs were castrated within 2 weeks of birth. All orchidectomized lambs (wethers) were housed in an open-sided barn under natural lighting with free access to water and alfalfa pellets supplemented with cereal grains and vitamin and mineral premix. Wethers were 6–8 months of age (bodyweight = 50–60 kg) at the time of experimentation. These studies were conducted during October and early November, a period of high reproductive activity in female sheep at this latitude (38°N). All experimental procedures involving the use of animals were conducted in accordance with National Institutes of Health (NIH) Guidelines and were reviewed and approved by the Animal Use and Care Committee for the University of California.

2.2. Cannulation

Prior to experimentation, two polyethylene cannulae (Intramedic PE 190, Clay Adams, Parsippany, NJ) were inserted into the left jugular vein to serve as hormone-delivery cannulae. A third cannula was inserted into the contralateral vein and used for blood collection. All cannulae were passed through a protective plastic tubing sheath along the halter and lead rope to the exterior of the animal holding area. Animals were freely mobile at the end of a 1-m lead. The cannulae were inserted 3 days prior to initiation of treatment to permit acclimation to the conditions of experimentation.

2.3. Hormone delivery

Cannulae for the delivery of cortisol or oestradiol were connected to syringes placed in Harvard infusion pumps (Model 2265, Harvard Bioscience, South Natick, MA). Cortisol (Sigma, St. Louis, MO) in 50% ethanol–saline (cortisol delivery vehicle) and/or oestradiol (Sigma) in 10% ethanol–saline (oestradiol delivery vehicle) were delivered by continuous infusion.

2.4. Experimental procedure

The effect of cortisol and oestradiol on gonadotropin secretion and pituitary concentrations of GnRH receptor and GnRH receptor mRNA was examined using 24 wethers assigned at random to one of the four treatment groups in a 2 × 2 factorial design (n = 6 wethers/group). Twelve wethers received cortisol (90 μg/kg/h; groups 2 and 4) or a comparable volume of vehicle (groups 1 and 3) by continuous infusion for 48 h. Preliminary studies demonstrated that intravenous delivery of cortisol at this rate resulted in stable serum concentrations of cortisol of 75–90 ng/ml. During the final 24 h of infusion, wethers also received oestradiol (6 ng/kg/h; groups 3 and 4) or a comparable volume of vehicle (groups 1 and 2). Blood samples were collected at 4-h intervals during the 48-h infusion period. The amplitude and frequency of secretory
pulses of LH were assessed in blood samples collected during a 3-h period of intensive blood collection (10-min collection interval) beginning 21 h after initiation of oestradiol infusion. At the end of infusion, animals were stunned by means of a captive bolt pistol and killed by exsanguination. Anterior pituitary tissue was quickly excised, halved by a mid-sagittal cut and immediately frozen in liquid nitrogen and stored at $-80^\circ C$ for later analysis. Blood was allowed to clot on ice and serum was harvested within 24 h of sample collection. Serum samples were rapidly frozen and stored at $-20^\circ C$ for later endocrine analysis.

2.5. Endocrine analysis

Tissue and/or serum concentrations of LH, FSH, oestradiol and cortisol were determined by use of previously validated procedures (Adams et al., 1975, 1988; Sakurai et al., 1992; Daley et al., 1999b). The LH (NIAMDD-oLH-26) and FSH (NIAMDD-oFSH-RP-1) reference standards were gifts from the National Hormone and Pituitary Program (Baltimore, MD). In all cases, intra- and interassay coefficients of variation were < 10%. The minimum sensitivity of the LH, FSH, oestradiol, and cortisol assays was 0.1 ng/ml, 0.25 ng/ml, 0.6 pg/ml, and 1.0 ng/ml, respectively.

The affinity and tissue concentration of GnRH receptor were determined by use of the procedure previously described (Sakurai and Adams, 1991; Sakurai et al., 1993). Tissue concentrations of mRNA for the LH$\beta$ and FSH$\beta$ subunits and GnRH receptor mRNA were determined by use of the solution hybridization RNase protection procedures described previously (Sakurai et al., 1993; Adams et al., 1996). Plasmids containing cDNA inserts for the bovine LH$\beta$ (Maurer, 1985) and FSH$\beta$ (Maurer and Beck, 1986) subunits were provided by Dr. R. Maurer (Department of Cell Biology and Anatomy, Oregon Health Sciences University, Portland, OR). A plasmid containing a cDNA insert for the ovine GnRH receptor (Brooks et al., 1993) was kindly provided by Dr. J. Brooks (MRC Reproductive Biology Unit, Edinburgh). The sense and antisense cRNAs were generated by in vitro transcription using either T7 RNA or SP6 RNA polymerase and the Riboprobe Gemini System II reagent system (Promega, Madison, WI).

2.6. Statistical analyses

Wethers were assigned to one of the four cells in a $2 \times 2$ factorial experiment, with the main effects being cortisol and oestradiol infusion. Data were analyzed by ANOVA (Gill, 1978). Where significant treatment effects were noted, mean comparisons were made using Duncan’s Multiple Range test. Data are presented in the text, table and figures as means $\pm$ SEM. The frequency and amplitude of secretory episodes of LH were evaluated using the criteria of Goodman and Karsch (1980). The basal level of LH was defined as the serum concentration of LH noted immediately before a pulse of LH secretion. The amplitude of a secretory pulse was defined as the concentration of LH at the peak less the concentration at the preceding nadir.
3. Results

3.1. Serum concentrations of cortisol

Continuous delivery of cortisol at a rate of 90 μg/kg/h increased serum concentration of cortisol to 80 ± 2 ng/ml within 4 h of initiation of infusion. Serum concentration of cortisol was maintained at this level for the remainder of cortisol delivery. In contrast, serum concentration of cortisol in wethers receiving vehicle alone did not differ from pretreatment concentrations (20 ± 1 ng/ml). Serum concentrations of cortisol at the end of the infusion period were 77 ± 8 and 18 ± 5 ng/ml in wethers receiving cortisol or vehicle, respectively.

3.2. Serum concentrations of oestradiol

Although oestradiol was not detectable (< 0.6 pg/ml) in wethers receiving vehicle alone, continuous infusion of oestradiol at 6 ng/kg/h increased serum concentration of oestradiol to 2.5 ± 0.1 pg/ml 4 h after beginning oestradiol administration. Serum concentration of oestradiol was maintained at this level throughout the remainder of the oestradiol infusion period. Serum concentration of oestradiol in oestradiol-treated wethers was not affected (P > 0.05) by concurrent infusion of cortisol or cortisol delivery vehicle.

3.3. Serum concentrations of LH and FSH

Serum concentration of LH during the first 24 h of infusion did not differ (P > 0.05) in wethers receiving cortisol or the cortisol delivery vehicle. Similarly, at the beginning of the oestradiol infusion period serum concentrations of LH were comparable (P > 0.05) in wethers receiving cortisol (3.3 ± 0.6 ng/ml) or vehicle alone (3.9 ± 0.3 ng/ml; Fig. 1). Continued infusion of cortisol or vehicle for an additional 24-h period did not

![Fig. 1. Serum concentrations of LH in orchidectomized sheep (wethers) receiving cortisol (90 μg/kg/h; ○, ●) or a comparable volume of cortisol delivery vehicle (50% ethanol–saline; △, ▲) during a 48-h infusion period. Twelve wethers were included in both the cortisol and vehicle infusion groups. During the final 24 h of infusion, six wethers from each of the cortisol and vehicle infusion groups received concurrent oestradiol (6 ng/kg/h; ●, ▲) or oestradiol delivery vehicle (10% ethanol–saline; ○, △) by continuous infusion. Values denoted with asterisk differed (P < 0.05) from values in animals (△) receiving vehicle alone.](image-url)
significantly affect serum concentration of LH. Similarly, mean serum concentration of LH in wethers was not significantly affected by infusion of oestradiol alone. However, concurrent infusion of cortisol and oestradiol significantly decreased mean serum concentration of LH relative to LH levels in control animals receiving vehicle alone. Indeed, at the end of the infusion period the serum concentration of LH in wethers receiving cortisol and oestradiol (2.2 ± 0.2 ng/ml) was significantly reduced (\( P < 0.05 \)) relative to the final serum concentration of LH in control wethers (4.5 ± 0.7 ng/ml). In contrast, the final serum concentration of LH in wethers receiving cortisol or oestradiol alone (3.7 ± 0.6 and 3.7 ± 0.4 ng/ml, respectively) did not differ (\( P > 0.05 \)) from the final LH concentration in control animals. Conversely, the final serum concentration of FSH in control wethers (9.7 ± 1.1 ng/ml) did not differ (\( P > 0.05 \)) from values noted in wethers receiving cortisol (9.6 ± 1.3 ng/ml) or oestradiol (7.8 ± 1.0 ng/ml) alone, or in combination (9.2 ± 0.9 ng/ml).

3.4. Pattern of LH secretion

Although the frequency of secretory episodes of LH in wethers receiving cortisol or oestradiol alone did not differ (\( P > 0.05 \)) from pulse frequency in control wethers, LH pulse frequency was reduced in animals receiving cortisol and oestradiol concurrently (Table 1). Similarly, the amplitude of secretory episodes of LH was not affected by intravenous delivery of cortisol or oestradiol alone. However, pulse amplitude was significantly augmented in wethers receiving cortisol and oestradiol in combination. Conversely, basal or nadir concentrations of LH were decreased (\( P < 0.05 \)) during concurrent infusion of cortisol and oestradiol.

3.5. Pituitary concentrations of GnRH receptor and GnRH receptor mRNA

Concentrations of GnRH receptor and GnRH receptor mRNA in pituitary tissue of wethers receiving oestradiol were significantly increased relative to tissue levels of

Table 1
The effect of continuous infusion of cortisol (90 μg/kg/h) or a comparable volume of cortisol delivery vehicle (50% ethanol–saline) for 48 h on the pattern of LH secretion in wethers receiving oestradiol (6 ng/kg/h) or oestradiol delivery vehicle (10% ethanol–saline) during the final 24 h of the infusion period

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( n )</th>
<th>LH pulse frequencya (pulses/3 h)</th>
<th>Pulse amplitude (ng/ml)</th>
<th>Basal LH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>6</td>
<td>3.0 ± 0.2b</td>
<td>2.4 ± 0.3b</td>
<td>3.3 ± 0.1b</td>
</tr>
<tr>
<td>Cortisol</td>
<td>6</td>
<td>2.5 ± 0.2b,c</td>
<td>1.9 ± 0.2b</td>
<td>2.8 ± 0.2b,c</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>6</td>
<td>3.2 ± 0.2b</td>
<td>2.6 ± 0.3b</td>
<td>2.4 ± 0.2b,c</td>
</tr>
<tr>
<td>Cortisol + oestradiol</td>
<td>6</td>
<td>2.2 ± 0.2c</td>
<td>4.2 ± 0.4c</td>
<td>2.2 ± 0.1c</td>
</tr>
</tbody>
</table>

aThe pattern of LH secretion was assessed during a 3-h window of intensive blood collection (10-min collection interval) beginning 21 h after initiation of oestradiol infusion. Pulse amplitude is defined as the concentration of LH at the peak less the concentration at the preceding nadir.

b,c Values (means ± SEM) in a column that do not share a common superscript differ significantly (\( P < 0.05 \)).
Fig. 2. Effect of cortisol and/or oestradiol on steady state concentrations of GnRH receptor and GnRH receptor mRNA in pituitary tissue of orchidectomized sheep (wethers). Wethers received either cortisol (Cortisol; 90 μg/kg/h; n = 12) or a comparable volume of cortisol delivery vehicle (Control; 50% ethanol–saline; n = 12) during a 48-h infusion period. During the final 24 h of infusion, six wethers from each of the Control and Cortisol infusion groups received concurrent oestradiol (Oestradiol; 6 ng/kg/h) or oestradiol delivery vehicle (Vehicle; 10% ethanol–saline) by continuous infusion. Anterior pituitary tissue was collected at the end of the infusion period. Tissue concentrations of GnRH receptor or GnRH receptor mRNA that do not share a letter designation differ significantly \( P < 0.05 \). FTE, fresh tissue equivalent.

GnRH receptor and receptor mRNA noted in vehicle-infused control animals (Fig. 2). Although continuous infusion of cortisol did not significantly affect basal concentrations of GnRH receptor or GnRH receptor mRNA, the oestradiol-induced augmentation of GnRH receptor and receptor mRNA was significantly reduced in wethers receiving cortisol and oestradiol in combination.

3.6. Tissue concentrations of LH and FSH and gonadotropin subunit mRNA

Although infusion of oestradiol alone did not significantly affect pituitary tissue concentrations of LH and LHβ mRNA, both measures of gonadotrope function were significantly increased after 48 h of cortisol infusion (Table 2). In contrast, tissue concentrations of LH and LHβ mRNA in wethers receiving cortisol and oestradiol concurrently did not differ \( P > 0.05 \) from values noted in control wethers. Similarly, pituitary stores of FSH in wethers receiving cortisol or oestradiol alone, or in combination, did not differ \( P > 0.05 \) from the tissue concentration of FSH noted in control wethers receiving vehicle alone. Tissue concentration of FSHβ mRNA in wethers...
Table 2
The effect of continuous infusion of cortisol (90 μg/kg/h) or a comparable volume of cortisol delivery vehicle (50% ethanol–saline) for 48 h on pituitary tissue concentrations of LH and FSH and steady-state concentrations of LHβ and FSHβ mRNA in wethers receiving oestradiol (6 ng/kg/h) or oestradiol delivery vehicle (10% ethanol–saline) during the final 24 h of the infusion period

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Tissue LH (μg mg⁻¹ FTE)</th>
<th>LHβ mRNA (pg/μg total RNA)</th>
<th>Tissue FSH (ng/mg FTE)</th>
<th>FSHβ mRNA (pg/μg total RNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>6</td>
<td>0.51 ± 0.09b</td>
<td>19.3 ± 1.4b</td>
<td>66.5 ± 11.9</td>
<td>3.2 ± 0.4b</td>
</tr>
<tr>
<td>Cortisol</td>
<td>6</td>
<td>0.81 ± 0.07c</td>
<td>31.9 ± 3.4c</td>
<td>87.3 ± 9.8</td>
<td>5.6 ± 0.4c</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>6</td>
<td>0.60 ± 0.07b</td>
<td>13.3 ± 1.6b</td>
<td>71.1 ± 7.6</td>
<td>3.0 ± 0.5c</td>
</tr>
<tr>
<td>Cortisol + oestradiol</td>
<td>6</td>
<td>0.60 ± 0.03b</td>
<td>21.1 ± 3.0b</td>
<td>77.8 ± 2.0</td>
<td>4.8 ± 0.7b+c</td>
</tr>
</tbody>
</table>

a FTE, fresh tissue equivalent.
b,c Values (means ± SEM) in a column that do not share a common superscript differ significantly (P < 0.05).

receiving oestradiol alone did not differ (P > 0.05) from values noted in control animals. Conversely, continuous infusion of cortisol for 48 h significantly increased tissue concentrations of FSHβ mRNA.

4. Discussion

In the work presented here, we examine the effect of short-term infusion of cortisol on gonadotrope function. Although neither cortisol nor oestradiol alone affected the pattern of LH secretion, concurrent administration of oestradiol and stress-like concentrations of cortisol resulted in a significant reduction in serum concentrations of LH and suppression of LH pulse frequency. These observations are consistent with the response noted in wethers after more prolonged infusion of cortisol (Daley et al., 1999b). A similar glucocorticoid-induced response has also been reported in rodents (Vreeburg et al., 1984, 1988). Collectively, these studies suggest that both short-term and chronic administration of stress-like concentrations of cortisol increase the negative feedback effect of oestradiol. We postulate that the reduced fertility associated with stress may reflect, at least in part, cortisol-dependent enhancement of the negative feedback potency of oestradiol, which results in reduced activity of the hypothalamic GnRH pulse generating system and decreased gonadotropin secretion.

This postulate is supported by recent reports indicating that the activity of GnRH-containing neurons and episodic release of GnRH are suppressed during periods of stress (Chen et al., 1992; Battaglia et al., 1997; Nappi and Rivest, 1997). It is interesting to note that this response to stress is particularly acute during the follicular phase of the reproductive cycle and less prominent in ovariectomized animals (Chen et al., 1992) or animals in the luteal phase (Norman et al., 1994). Moreover, ovariectomized animals are made increasingly sensitive to the suppressive effects of stress by concurrent treatment with oestradiol (Chen et al., 1992). Taken together, these observations indicate that the extent of stress-induced suppression of the GnRH pulse generating system varies with gonadal status.
Tissue concentration of GnRH receptor is generally considered to be one of several, key determinants of gonadotrope responsiveness (Conn et al., 1987; Stojilkovic et al., 1994) and oestrogen-dependent augmentation of tissue concentration of GnRH receptor is associated with enhanced responsiveness (Sakurai and Adams, 1991). The results presented here demonstrate that basal concentrations of GnRH receptor and GnRH receptor mRNA are not affected by cortisol. This is consistent with the response noted in rodents (Suter et al., 1988; Rosen et al., 1991). In contrast, the observations reported here indicate that short-term (48 h) exposure to stress-like concentrations of cortisol significantly reduced the magnitude of oestradiol-dependent increase in tissue levels of GnRH receptor and GnRH receptor mRNA. This glucocorticoid-dependent reduction in GnRH receptor expression appears to be dependent on the magnitude and duration of oestradiol stimulation. Indeed, our recent studies demonstrate that cortisol-dependent suppression of the oestrogenic response is attenuated by increasing the duration or level of oestrogenic stimulation (Adams et al., 1999; Daley et al., 1999b). Although the mechanism underlying this glucocorticoid-dependent response cannot be precisely defined using our in vivo model system, recent in vitro studies indicate that glucocorticoids decrease gene transcription and reduce mRNA stability in pituitary tissue (Gothard et al., 1996; Iredale and Duman, 1997). One, or both, of these glucocorticoid mediated responses may account for the reduction in oestrogen-induced increase in GnRH receptor mRNA in wethers receiving stress-like concentrations of cortisol.

Although cortisol alone did not affect the basal concentration of GnRH receptor mRNA, stress-like concentrations of cortisol significantly increased the steady state concentration of FSHβ mRNA. A similar increase in tissue concentrations of FSHβ mRNA has been noted in rodents after glucocorticoid stimulation (Ringstrom et al., 1991; McAndrews et al., 1994). This apparently reflects a direct effect of glucocorticoids on gonadotrope cells to increase gene transcription (Kilen et al., 1996).

In addition to increasing pituitary concentrations of FSHβ mRNA, we noted that stress-like concentrations of cortisol increased pituitary stores of LH and steady-state concentrations of LHβ mRNA. Cortisol-dependent augmentation of tissue concentrations of LH and LHβ mRNA was not evident in wethers receiving cortisol and oestradiol in combination. This suggests that oestradiol may suppress the glucocorticoid-induced response. This response appears to be affected by the duration of glucocorticoid stimulation since prolonged cortisol administration results in increased tissue stores of LH even in the face of concurrent oestradiol stimulation (Daley et al., 1999b). Although glucocorticoids do not affect tissue concentrations of LHβ mRNA in the rodent model (Ringstrom et al., 1991; Kilen et al., 1996), an increase in pituitary stores of LH was noted in cortisol-treated rodents (Ringstrom et al., 1991). The glucocorticoid-dependent augmentation of tissue concentrations of LHβ and FSHβ mRNA noted in our study is consistent with the postulate that stress-induced secretion of glucocorticoids enhances gonadotropin synthesis and storage in preparation for the resumption of reproductive activity after return of the stress-free condition (McAndrews et al., 1994).

Stressful stimuli mobilize an array of endocrine factors (Coleman et al., 1993; Battaglia et al., 1998), all of which may contribute to stress-induced infertility. However, the complex and multifaceted nature of the response to stress makes it difficult to
establish a specific casual link between stress and infertility. In the studies described here, we attempt to minimize this problem by confining our focus to the impact of cortisol on reproductive function. The important role of cortisol in stress-induced infertility is indicated by our recent observation that continuous delivery of stress-like concentrations of cortisol prevents or delays ovulation in sheep (Daley et al., 1999a). The observations reported here indicate that stress-like concentrations of cortisol may act at both hypothalamic and pituitary sites to exert this anti-gonadal effect. Cortisol, acting at hypothalamic sites, appears to enhance the negative feedback response induced by oestradiol. Similarly, cortisol acts at hypophyseal sites to reduce oestrogen-dependent increase in tissue concentrations of GnRH receptor and receptor mRNA. The combined effect of glucocorticoid action at both hypothalamic and hypophyseal sites would likely decrease gonadotropin secretion and depress fertility.

References


