Modulation of ovine fetal adrenocorticotropin secretion by androstenedione and 17β-estradiol

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Saoud, Christine J., and Charles E. Wood. Modulation of ovine fetal adrenocorticotropin secretion by androstenedione and 17β-estradiol. *Am. J. Physiol.* 272 (*Regulatory Integrative Comp. Physiol.* 41): R1128–R1134, 1997.—Parturition in sheep is initiated by increases in activity of the fetal hypothalamic-pituitary-adrenal axis. We have previously reported that cortisol negative feedback efficacy is decreased at the end of gestation. The present study was designed to test the hypothesis that increasing plasma estrogen and/or androgen concentrations in the fetus might increase plasma adrenocorticotropic hormone (ACTH) concentration, either by stimulating ACTH secretion or by altering the negative feedback effect of cortisol on ACTH. Fetal sheep were chronically catheterized and treated with no steroid (control), 17β-estradiol, or androstenedione (each ~0.24 mg/day). After catheterization and implantation of steroid pellet, fetuses were subjected to two short (10 min) periods of sodium nitroprusside-induced hypotension with or without pretreatment with intravenous infusion of hydrocortisone sodium succinate (0.5 μg/min) to test fetal ACTH responsiveness to stress and cortisol negative feedback efficacy. Estradiol treatment significantly increased basal plasma ACTH and cortisol concentrations relative to control fetuses but did not interfere with the inhibition of ACTH secretion by cortisol. Fetal plasma ACTH responses to hypotension were significantly suppressed ~60% in both control and estradiol-treated groups. Androstenedione treatment significantly increased basal fetal plasma ACTH and decreased basal fetal plasma cortisol concentration. Androstenedione did not alter stimulated levels of fetal ACTH but did block the inhibition of stimulated ACTH by cortisol. We conclude that increased fetal cortisol and ACTH secretion at the end of gestation may be due to the combined effects of the gonadal steroids in that estradiol increases basal plasma ACTH secretion while androstenedione reduces cortisol negative feedback efficacy.

adrenocorticotropic hormone; cortisol; negative feedback; fetal sheep; parturition

IN FETAL SHEEP, parturition is stimulated by increases in fetal hypothalamic-pituitary-adrenal (HPA) axis activity (6, 21). Before spontaneous parturition, the activity of the fetal HPA axis increases (1, 30, 33, 39) activity that is dependent on the integrity of the paraventricular nuclei of the fetal hypothalamus (11, 27–29). Parturition can be prevented or delayed by destruction of the paraventricular nuclei (11, 25) or pituitary (22–24) or stimulated by infusions of adrenocorticotropic hormone (ACTH) (19, 20) or glucocorticoids (13, 41). Understanding the mechanism of the increased fetal HPA axis activity at the end of gestation is key to understanding the mechanism of spontaneous parturition in this species. We have previously demonstrated that fetal sheep between 120 and 130 days gestation are very sensitive to cortisol negative feedback of ACTH secretion (38) but then become relatively insensitive to the effects of cortisol near term (39). We have proposed that this decrease in cortisol negative feedback efficacy after 135 days gestation may be important for the generation of the preparturient increase in plasma ACTH and cortisol (39). The mechanism of this change in negative feedback has not been identified. It is possible that the increases in fetal plasma estrogen and/or androgen concentrations might be involved.

Studies in adult animals have shown that estrogen increases the activity of the HPA axis. Female rats have higher basal and stimulated plasma corticosterone levels than male rats (17), and female rats during proestrus have enhanced plasma ACTH and corticosterone responses to stress (36). Several groups have shown that ovariectomy in rats results in decreased plasma ACTH bioactivity and corticosterone responses to stress that can be reversed by exogenous estrogen replacement (4, 8, 18). Because estrogens and androgens increase before parturition and estrogens are known to interact with the HPA axis, we proposed that androgens or estrogens might influence fetal ACTH secretion at the end of gestation.

These experiments were designed to investigate the effects of exogenous androstenedione and 17β-estradiol on ACTH secretion in the late gestation fetal sheep. These steroids were chosen because they are naturally occurring steroids whose concentrations are increased at the end of gestation. Specifically, we tested the hypothesis that elevations of fetal androstenedione or estradiol increase plasma ACTH secretion by altering cortisol negative feedback of ACTH.

MATERIALS AND METHODS

Animals. Twenty-five time-dated pregnant ewes were studied. Seventeen of these ewes were included in all aspects of this protocol. An additional eight ewes were included as supplementary animals used to estimate the effect of hormone pellet implantation on fetal plasma steroid concentrations. Of the animals subjected to the complete protocol, 11 ewes carried singleton fetuses and 6 ewes carried twins. In the supplementary group, all eight ewes carried singleton fetuses.

Fetal surgery. Aseptic surgery was performed for chronic implantation of vascular and amniotic fluid catheters and steroid pellets on *day 122 ± 0.9* (estradiol-treated group), *day 120.0 ± 1.1* (androstenedione-treated group), or *day 122.4 ± 1.0* (control group) of gestation (term is ~148 days in uncatheterized fetal sheep). For 24 h before surgery, the ewes were allowed free access to water but were not permitted food. During surgery, the ewes and fetuses were anesthetized with halothane or isoflurane (0.5–3.0%) in oxygen. Fetal and maternal arterial and venous catheters and an amniotic fluid catheter were placed as previously described (38, 39). At the time of catheter placement, a pellet containing 5 mg andro-

stenedione or 17β-estradiol (Innovative Research of America, Toledo, OH) was implanted subcutaneously in the area of the gluteus medius. These pellets were designed to release their steroid content in 21 days. Control fetuses were catheterized but did not receive a pellet implant. Each fetus received 750 mg ampicillin via the amniotic fluid at the time of surgery and again each day the vascular catheters were flushed. The ewes received 750 mg ampicillin intramuscularly postoperatively twice daily for 5 days. Catheters were flushed and reheparinized at the time of blood collection or experimentation (at least once every 3 days).

In each of the six ewes carrying twins, one twin received a pellet and the other twin was a control fetus (3 estradiol and 3 androstenedione, each with a twin control). Eight singleton fetuses received pellets (5 estradiol and 3 androstenedione), and three were control fetuses.

Experimental protocol. Twenty-three fetuses were subjected to an experimental protocol designed to test fetal ACTH responsiveness to stimulation and to test for alterations in cortisol negative feedback sensitivity. All experiments were started between 0900 and 1000 to minimize possible variation in hormone concentrations between experiments. Each fetus was subjected to either one or two experiments. In fetuses subjected to two experiments, at least 48 h were allowed between the first and second experiment. On the morning of an experiment, the ewes were loaded into a study cart and transported (in pairs) to the laboratory from the animal resources facility. Catheters were flushed and connected to transducers (Statham P23 Id, Statham Instruments, Oxnard, CA) for measurement of fetal arterial and amniotic pressure. One hour was then allowed for the ewes to acclimate to their environment.

In each experiment, vehicle (0.9% saline) or cortisol (hydrocortisone sodium succinate; 6.0 μg/ml in 0.9% saline; Upjohn, Kalamazoo, MI) was infused into the fetal inferior vena cava at a rate of 5.1 ml/h for 2 h. One hour after the end of the vehicle or cortisol infusion, sodium nitroprusside (Elkins-Sinn, Cherry Hill, NJ) was infused into the fetal inferior vena cava for 10 min at a rate of 50 μg/min (0.5 ml/min) using a constant infusion syringe pump (model 341A; Sage Instruments, Orion Research, Cambridge, MA). Blood samples (5 ml) were drawn from the fetal and maternal arterial catheters at the beginning of the vehicle or cortisol infusion. Blood samples (3 ml) were drawn from the fetus after 1 and 2 h of vehicle or cortisol infusion and 0, 10, and 20 min after the start of the nitroprusside infusion. Blood samples were placed into chilled tubes containing EDTA (57 μg/ml blood). An additional fetal arterial blood sample (1 ml) was drawn anaerobically at the beginning of each experiment for measurement of fetal blood gases and pH (BMS3MK2 blood microsystem and PHM73 pH and blood gas analyzer; Radiometer, Copenhagen, Denmark). Blood samples for hormone analysis were kept on ice until they were centrifuged for 20 min at 3,000 *g*. After centrifugation, the plasma was transferred to a clean tube and stored at −20°C until hormones were assayed. Arterial and amniotic fluid pressures were measured during the final 20 min of the experiment with the use of a Grass model 7 recorder. The data were digitized and stored with an IBM AT microcomputer and a Keithley analog-to-digital converter on-line.

Not all of the 23 fetuses included in this protocol were subjected to both saline and cortisol infusion experiments. Seven fetuses were subjected to only one experiment because of spontaneous delivery ($n = 3$), complications not related to the experiment ($n = 3$), and pump failure ($n = 1$). Although not all fetuses were studied in all parts of the experimental design, all fetuses were healthy when they were studied (Table 1).

A supplemental group of eight fetuses was subjected to surgical implantation ($n = 2$) or sham implantation ($n = 6$) of androstenedione pellets and were allowed to recover from surgery as described above. These fetuses were not subjected to saline, cortisol, or nitroprusside infusion. They were used only to test the effect of pellet implantation or sham pellet implantation on fetal plasma estradiol and androstenedione concentrations.

Analysis of blood samples. Plasma ACTH, cortisol, and estradiol concentrations were measured by radioimmunoassay (RIA) as previously described (3, 14, 40). The antiserum used in the ACTH assay binds proopiomelanocortin and 22-kDa "pro-ACTH" as well as fully processed ACTH (34, 35). Estimates of plasma concentration using this assay therefore reflect all forms of ACTH immunoreactivity secreted by the fetal pituitary (26). Plasma androstenedione concentrations were measured using a commercial RIA kit (Diagnostic Products, Los Angeles, CA). Plasma ACTH and cortisol concentrations were measured in all plasma samples; androstenedione and estradiol were measured in the first plasma sample drawn in each experiment. In the fetuses subjected to the complete protocol, the volume of plasma available for analysis was limited. In these fetuses, we measured plasma androstenedione concentrations in all fetuses treated with androstenedione, but only in three control fetuses. Androstenedione was measured after extraction with ethyl acetate: hexane (3:2), and estradiol was measured after extraction with ethyl ether. The antiestradiol antiserum has an ~10% cross-reactivity with estrone (unpublished observations); accordingly, we separated estradiol and estrone in each plasma extract using Sephadex LH-20 columns according to an established protocol (Isolab, Akron, OH). Samples were evaporated to dryness, reconstituted in assay buffer, and run as previously described. All estradiol samples were run in a single assay, as were the androstenedione samples.

Calculations and statistic analyses. Fetal mean arterial pressure was corrected by subtraction of amniotic fluid pressure. Data were analyzed using one- and two-way analysis of variance (ANOVA) for equal or nearly equal "*n*" corrected for repeated measures in one dimension (time) (37). The two-way ANOVA was used to compare values of experimental variables in saline- and cortisol-infusion experiments within each treatment group (i.e., control, androstenedione, and estradiol treatment groups). Three-way ANOVA was used to assess the effect of estradiol or androstenedione treatment on fetal plasma ACTH and cortisol concentrations. A posteriori pairwise testing of differences between group means was performed using Duncan's multiple-range test

Table 1. *Fetal blood gases and pH at time of experimentation*

	n	Pa_{O_2}, mmHg	Pa_{CO_2}, mmHg	pH_a
Androstenedione + saline	6	21.3 ± 1.5	49.8 ± 3.1	7.348 ± 0.008
Androstenedione + cortisol	6	22.1 ± 1.5	48.8 ± 2.9	7.334 ± 0.009
Estradiol + saline	5	24.2 ± 2.1	43.2 ± 1.0	7.331 ± 0.023
Estradiol + cortisol	7	21.3 ± 1.6	43.1 ± 0.9	7.346 ± 0.014
Control + saline	8	25.1 ± 1.2	45.7 ± 2.2	7.337 ± 0.008
Control + cortisol	8	21.4 ± 1.2	45.0 ± 2.6	7.350 ± 0.012

Values are means ± SE; n = no. of experiments. Arterial P_{O_2} (Pa_{O_2}), P_{CO_2} (Pa_{CO_2}), or pH (pH_a) in control, estradiol-treated, and androstenedione-treated fetuses before and during intravenous infusion of saline are shown.

Table 2. *Plasma cortisol and ACTH concentrations during cortisol or saline infusions*

Time, min	Androstenedione + Saline	Androstenedione + Cortisol	Estradiol + Saline	Estradiol + Cortisol	Control + Saline	Control + Cortisol
			Fetal plasma cortisol concentrations, ng/ml			
−180	2.32 ± 0.5	3.61 ± 1.0	15.5 ± 4.9	17.4 ± 2.5	6.10 ± 1.2	8.00 ± 2.0
−120	1.91 ± 0.4	7.07 ± 3.6	25.4 ± 9.8	17.9 ± 3.0	7.04 ± 1.9	14.1 ± 3.6
−60	1.74 ± 0.2	7.35 ± 3.2	29.3 ± 13.4	15.6 ± 2.3	5.62 ± 1.6	13.1 ± 3.4
			Fetal plasma ACTH concentrations, pg/ml			
−180	199 ± 13	182 ± 15	846 ± 618	123 ± 27	127 ± 39	88 ± 21
−120	192 ± 17	167 ± 14	1,508 ± 786	94 ± 19	107 ± 28	142 ± 22
−60	156 ± 15	187 ± 11	1,444 ± 569	117 ± 37	109 ± 33	163 ± 17

Values are means ± SE. Plasma cortisol and ACTH concentrations were measured before (−180 min), during (−120 min), and at the end (−60 min) of a 120-min infusion of cortisol (0.5 μg/min). Times are expressed as relative to nitroprusside infusion (0 min).

(10). A significance level of 0.05 was used to reject the null hypothesis in all tests. Values are reported as means ± SE.

RESULTS

Blood gases. Fetal arterial blood gases and pH before the start of experiments are reported in Table 1. The values in each group are similar to blood gases that we have reported in healthy fetuses in previous experiments (38, 39).

Fetal plasma estradiol and androstenedione concentrations. Plasma estradiol concentrations were significantly increased in the estradiol-treated fetuses (51.6 ± 5.5 pg/ml, $n = 7$) compared with control fetuses (26.0 ± 5.1 pg/ml, $n = 12$), and fetal plasma androstenedione concentrations were significantly increased in androstenedione-treated fetuses (286 ± 27 pg/ml, $n = 9$) compared with control fetuses (230 ± 9 pg/ml, $n = 8$).

Basal fetal plasma ACTH and cortisol concentrations and responses to saline and cortisol infusions. Plasma concentrations of ACTH and cortisol before, during, and after infusion of saline or cortisol are reported in Table 2. When analyzed by three-way ANOVA corrected for repeated measures, the mean plasma ACTH and cortisol concentrations in estradiol-treated fetuses were significantly higher than in either control or androstenedione-treated fetuses. Androstenedione treatment significantly increased fetal plasma ACTH concentration compared with control fetuses and decreased fetal plasma cortisol concentration compared with both control and estradiol-treated fetuses (Table 2). The influence of estradiol treatment on plasma ACTH in saline-infused fetuses before the start of nitroprusside infusion is illustrated in Fig. 1.

The infusion of cortisol produced small increases in fetal plasma cortisol concentrations that were sometimes masked by the changes in fetal HPA axis activity produced by the estradiol treatment. In both the control and the androstenedione-treated fetuses, cortisol infusion produced statistically significant increases, and saline infusion did not produce any changes in fetal plasma cortisol concentration (Table 2). In the estradiol-treated fetuses, however, there were spontaneous, statistically significant ($P < 0.05$) increases in fetal plasma concentrations of cortisol during the infusion of saline. Because of this apparently spontaneous activity of the HPA axis, we measured no apparent increase in fetal

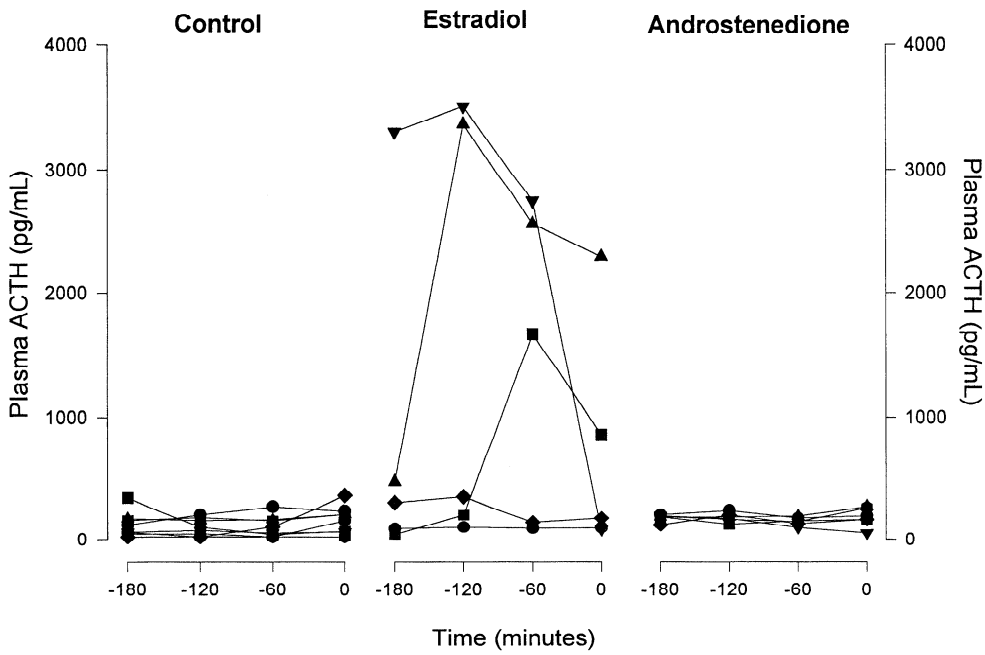

Fig. 1. Fetal plasma ACTH concentrations in individual control, estradiol-treated, and androstenedione-treated fetuses before and during intravenous infusion of saline (vehicle for cortisol infusion). Data from 5–8 individual animals depicted for each treatment.

plasma cortisol concentration during cortisol infusion, but a paradoxical increase in both ACTH and cortisol concentrations during saline infusion was noted (Table 2). The apparent increase in fetal plasma cortisol during saline infusion was accounted for by spontaneously increased fetal HPA axis activity in three of the five estrogen-treated fetuses in this experimental group.

ACTH and cortisol responses to nitroprusside infusion. Nitroprusside infusion decreased blood pressure equally in each treatment group (Fig. 2, *left*). Nitroprusside infusion significantly increased plasma ACTH concentrations (Fig. 2, *right*) after saline infusion (peak values of 1,237 ± 311 pg/ml, 2,239 ± 874 pg/ml, and 1,045 ± 429 pg/ml in androstenedione-treated, estradiol-treated, and control fetuses at 10 min, respectively). Peak fetal plasma ACTH values were significantly higher in the estradiol-treated fetuses compared with both control and androstenedione-treated fetuses. The induced changes (increases above initial values) in fetal plasma ACTH during hypotension were not significantly different among the three treatment groups.

The ACTH response to nitroprusside was significantly reduced by cortisol infusion in the control and estradiol-treated groups. Peak values measured after cortisol infusion in the control and estradiol-treated fetuses were significantly lower than peak values in each group after saline infusion (404 ± 92 vs 1,045 ± 429 and 888 ± 450 vs 2,239 ± 874 pg/ml, respectively). There was no significant difference between peak values after cortisol and saline infusion in the androstenedione-treated fetuses (957 ± 99 vs. 1,237 ± 311 pg/ml, respectively).

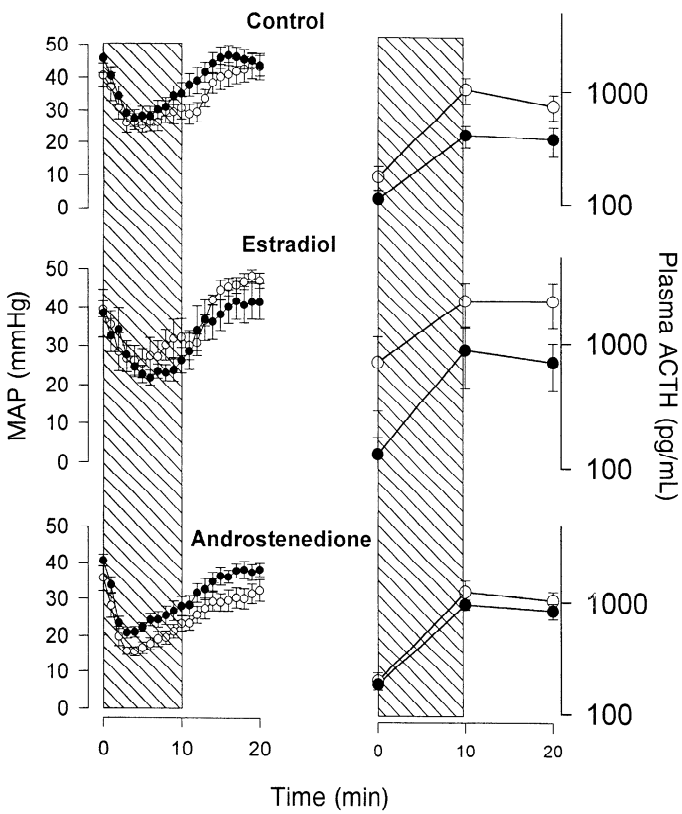

Fig. 2. Fetal mean arterial blood pressure (MAP; *left*) and fetal plasma ACTH concentrations (*right*; note logarithmic scale) before, during, and after nitroprusside infusion in sham control (*top*), estradiol-treated (*middle*), and androstenedione-treated (*bottom*) fetuses after saline (○) or cortisol (●) infusion. Nitroprusside was infused between 0 and 10 min (hatched area). Data are means + SE.

DISCUSSION

The results of this study demonstrate that *1*) estradiol augments fetal ACTH secretion and *2*) androstenedione decreases the efficacy of cortisol negative feedback inhibition of fetal plasma ACTH secretion. We proposed that the increase in HPA axis activity resulting from physiological increases in fetal plasma androgen and estrogen concentrations might be an important component in the preparturient increase in fetal ACTH and cortisol secretion at the end of gestation in this species.

The present results demonstrate a high sensitivity of the fetal HPA axis to estradiol and androstenedione. The release of estradiol or androstenedione from the implanted pellets (~238 μg/day or 9.9 μg/h, according to the manufacturer) elevated plasma estradiol and androstenedione concentrations ~25 and 56 pg/ml. These increases are well within the range of endogenous increases observed at the end of gestation (42).

The effect of the exogenous androstenedione appeared to be distinct from the effect of the exogenous estradiol. It is remarkable that, even though estradiol increased the basal and stimulated fetal plasma concentration of ACTH two- to threefold, cortisol suppressed stimulated fetal ACTH ~60% in both the estradiol-treated and control groups. This is consistent with the observation in adult animals that cortisol negative feedback suppression of ACTH responses to low- and moderate-intensity stimuli is essentially independent of stimulus intensity (15). On the other hand, the exogenous androstenedione eliminated cortisol negative feedback. We believe that the effect of androstenedione might be similar to the spontaneous reduction in cortisol negative feedback efficacy observed at the end of gestation (39).

These results are consistent with the known actions of estrogens in adult animals. In adult rats, ovariectomy has been shown to decrease both basal and ether-stimulated plasma ACTH concentrations and to decrease pituitary responsiveness to stimulation by hypothalamic extracts in vitro (8). Female rats have increased corticosterone responses to stress of exposure to ether vapors and have a greater adrenal responsiveness to exogenously administered ACTH compared with male rats (17). In ovariectomized rats, exogenously administered estradiol increased plasma ACTH bioactivity and adrenal responsiveness to ACTH (18) and increased plasma ACTH and corticosterone responses to stress (4, 36). However, our results differ from those of Burgess and Handa (4), who reported that estradiol administration to ovariectomized rats impaired glucocorticoid negative feedback inhibition of ACTH secretion. We found that androgen, not estrogen, impairs glucocorticoid negative feedback efficacy in the sheep fetus.

The effect of androgen on ovine fetal ACTH secretion also differs from that in the rat. Castration of male rats chronically increases both basal and stimulated plasma ACTH concentrations (9, 12). Treatment of castrated rats with testosterone (9, 12) or dihydrotestosterone (12) reversed this effect. It is therefore apparent that androgen is inhibitory to ACTH secretion in the male rat. The lack of effect of castration on hippocampal, hypothalamic, or pituitary corticosteroid receptors suggests no effect on corticosteroid negative feedback in rats (12). We have found that administration of androstenedione produces a modest increase in basal fetal plasma ACTH concentration and a modest decrease in basal fetal plasma cortisol concentration. Importantly, we believe, androstenedione does block corticosteroid negative feedback effects on ACTH. Whether this represents a species difference or, perhaps, a difference in experimental paradigm (intact fetal sheep exposed to both gonadal and placental steroids versus gonadectomized adult rats) cannot be addressed without further experiments.

The apparent stimulation of the fetal HPA axis by estradiol complicated the interpretation of the data by producing increases in fetal plasma ACTH and cortisol concentrations unrelated to the infusions of saline, cortisol, or nitroprusside. Specifically, three of the five estradiol-treated fetuses spontaneously increased fetal plasma ACTH during saline infusion (at −60 min: increases to 1,670, 2,560, and 2,742 pg/ml, as illustrated in Fig. 1). The result of this spontaneous HPA activity was elevated mean plasma ACTH concentrations at *time zero* in the saline-infused estradiol-treated fetuses compared with the cortisol-infused fetuses. We believe that spontaneous HPA activity also complicated measurement of changes in fetal plasma cortisol in the cortisol-infused group. We infused cortisol at a rate of 0.5 μg/min for 2 h, a dose that completely suppressed fetal ACTH responses to the same dose of nitroprusside when infused for 5 h (38). The increase in fetal plasma cortisol concentration expected during this infusion was small (38) and was completely obscured in the present experiments by the variable baseline in fetal cortisol in response to chronic estradiol treatment and the relatively infrequent blood sampling.

A preparturient increase in maternal and fetal plasma estrogen concentrations has been documented by a number of investigators, although the time course of this increase varies from study to study. Maternal unconjugated estrogens have been reported to increase over the last 40 h (32) to 4 days (2), with a very sharp increase immediately before parturition (5). In the fetus, a similar pattern has been reported for conjugated and unconjugated estrone (31); however, data in one study (7) demonstrated a more gradual increase in fetal and amniotic estradiol over ~8 days, with a rapid increase in fetal, maternal, and amniotic concentrations in the final 2 days of fetal life. Increases in estrogens are also seen during dexamethasone-induced parturition (16). The fetuses in this study were subjected to a chronic dose of 17β-estradiol over the course of ~2 wk, a pattern that does not faithfully mimic the pattern of plasma estradiol concentrations occurring endogenously at term in the fetal sheep. Although the present data cannot be interpreted as evidence that fetal plasma estradiol represents a "trigger" to parturition, the results suggest that estrogens play a facilitatory role in HPA axis activation at the end of gestation by increasing the magnitude of the ACTH responses to stimuli.

We conclude that exogenous androstenedione and 17β-estradiol in physiological concentrations modulate plasma ACTH secretion in late-gestation fetal sheep. Estrogen increased plasma ACTH both during nitroprusside-induced hypotension and during apparently "basal" conditions. Androstenedione decreased the negative feedback action of cortisol on ACTH secretion (demonstrated by the lack of suppression of the ACTH response to nitroprusside-induced hypotension after the infusion of cortisol). We therefore speculate that physiological increases in fetal plasma androgen and estrogen concentrations at the end of gestation might be an important component of the mechanism that results in parturition in this species.

Perspectives

The endocrine mechanism initiating parturition in the sheep, namely activation of the fetal HPA axis, is shared by other ruminants but is somewhat different than in the human being or other primates. In the sheep and other ruminants, cortisol induces cytochrome $P\text{-}450_{c17}$ in the placenta, which shifts placental steroidogenesis from a scheme favoring progesterone to a scheme favoring estrogens and androgens. In the human being and other primates, placental $P\text{-}450_{c17}$ is not induced by cortisol. The fetal adrenal, zonated into so-called "fetal" and "definitive" zones, secretes more dehydroepiandrosterone (DHEA) than cortisol. The DHEA secreted by the fetal zone in response to increased fetal plasma ACTH concentration is a precursor for placental estrogen biosynthesis. Thus the fetal HPA axis in the primate ultimately influences fetal plasma estrogen and androgen concentrations, although somewhat differently than as in the sheep. The onset of parturition in both species is heralded by increases in both HPA axis activity and sex steroid concentrations. It is possible, although perhaps debatable, that the fetal HPA axis is involved in triggering parturition in human beings and primates. If so, it is possible that increases in circulating fetal plasma estrogens and androgens might influence neuroendocrine processes common to both primates and ruminants and therefore modulate the timing of parturition in both species.

We thank Dr. Timothy Cudd for his expertise in surgical preparation and data acquisition. We also thank Dr. Pushpa Kalra and Dr. Maureen Keller-Wood for generously allowing us use of their laboratories and for giving us the benefit of their assay expertise.

This work was supported by National Institute of Child Health and Human Development Grant HD-24250 and was performed during the tenure of an Established Investigator Award from the American Heart Association.

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Received 28 March 1996; accepted in final form 14 October 1996.

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