Glucocorticoid modulation of cardiovascular and autonomic function in preterm lambs: role of ANG II

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Segar, Jeffrey L., Kurt A. Bedell, and Oliva J. Smith. Glucocorticoid modulation of cardiovascular and autonomic function in preterm lambs: role of ANG II. Am J Physiol Regulatory Integrative Comp Physiol 280: R646–R654, 2001.—The mechanisms by which antenatal glucocorticoids facilitate postnatal circulatory function in preterm infants are uncertain but may be related to augmented angiotensinergic functions. To test the hypothesis that the effects of glucocorticoids on postnatal cardiovascular and sympathetic activity are mediated via the renin-angiotensin system, we studied the effects of AT1 receptor blockade on postnatal changes in heart rate (HR), mean arterial blood pressure (MABP), renal sympathetic nerve activity (RSNA), and baroreflex control of HR in prematurely delivered lambs. After maternal administration of betamethasone (12 mg im 48 and 24 h before delivery), chronically instrumented preterm lambs (118- to 123-day gestation, term 145 days) were studied before and after delivery by cesarean section; fetuses received either the AT1 receptor antagonist losartan (10 mg iv, n = 6) or saline (n = 6) 1 h before delivery. A third group of animals (n = 6) received losartan without prior exposure to betamethasone. Compared with fetal values, betamethasone-treated animals demonstrated significant increases (P < 0.05) in MABP (47 ± 2 to 58 ± 2 mmHg) and RSNA (181 ± 80% of fetal value) 1 h after delivery. Betamethasone + losartan-treated lambs also displayed increases in MABP (48 ± 1 to 55 ± 3 mmHg) and RSNA (198 ± 96% of fetal value) 60 min after birth, similar to betamethasone alone lambs. Losartan alone treated animals had no postnatal increase in either MABP or RSNA; responses similar to those seen in nontreated sheep delivered at the same gestational age. The sensitivity of baroreflex-mediated changes in HR in response to increases in MABP was less in both groups of betamethasone-treated animals; no effect was seen with losartan. These results suggest the postnatal increases in MABP and RSNA seen with antenatal glucocorticoid treatment are not mediated by stimulation of peripherally accessible AT1 receptors. We speculate that augmented cardiovascular function in glucocorticoid-treated premature lambs is dependent, in part, on a generalized sympathoexcitatory response and that this effect of glucocorticoids is mediated by central mechanisms.

renal sympathetic nerve activity; betamethasone; blood pressure; heart rate; baroreflex; renin-angiotensin system

PREAMATURELY DELIVERED INFANTS born to mothers treated antenatally with glucocorticoids have improved clinical outcomes related primarily to steroid effects on lung maturity and function. However, nonpulmonary effects of antenatal glucocorticoids on the developing fetus and postnatal physiological adaptations are becoming increasing appreciated. Studies using maternal and/or direct fetal administration of glucocorticoids have demonstrated effects on postnatal blood pressure, cardiac output and contractility, and renal function (4, 8, 9, 22, 41, 42). The mechanisms by which antenatal glucocorticoids facilitate postnatal circulatory function are uncertain but may be related to augmented vascular, cardiac, neurohumoral, and autonomic functions.

We have previously shown in term fetal sheep that efferent sympathetic nerve activity increases at birth and likely contributes to the cardiovascular responses associated with the transition from fetal to newborn life (34). In contrast, this sympatoexcitation is absent after premature delivery, consistent with the impaired postnatal changes in circulatory function seen in these animals (33). Antenatal administration of glucocorticoids augment the sympathetic response after premature delivery and may be one mechanism by which maternal steroid administration improves postnatal cardiovascular homeostasis. The renin-angiotensin system is an important regulator of hemodynamic and fluid and electrolyte homeostasis during fetal and newborn life. Changes in the expression of several components of the renin-angiotensin system occur late during fetal development, and studies in newborn infants and animals have shown that the activity of the renin-angiotensin system increases at birth (15, 21, 29, 46, 49). Both circulating and locally produced ANG II influence the sympathetic nervous system and maintain sympathoexcitatory outflow by acting on ANG II type 1 (AT1) receptors within the central nervous system (for review see Refs. 24, 27). Glucocorticoids regulate the expression of several genes comprising the renin-angiotensin system and increase vascular responsiveness to ANG II (10, 14, 30). However, the interaction between glucocorticoids and the renin-angiotensin system and its effect on cardiovascular and autonomic function in premature newborns have not been evaluated. Therefore, we designed studies to investigate the role of AT1 receptor

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activation in mediating the blood pressure and autonomic effects of antenatal glucocorticoids in premature sheep. We compared these results with those previously published by our group in prematurely delivered lambs at similar gestational ages (33).

METHODS

Studies were performed in conscious, chronically instrumented fetal sheep at the gestational age of 118–123 days (term 145 days). Pregnant ewes of Dorset and Suffolk mixed breeding were obtained from a local source; gestational ages were based on the induced ovulation technique as previously described (17). Fetal body weight was estimated according to the following formula: fetal weight (kg) = 0.0961 × gestational age (days) − 9.228 (28). All surgical and experimental procedures were performed within the regulation of the Animal Welfare Act and the National Institutes of Health’s Guide for the Care and Use of Laboratory Animals. The Guiding Principles in the Care and Use of Animals approved by the Council of the American Physiological Society and governed by the Animal Care and Use Committee of the University of Iowa were strictly adhered to. At least 48 h were allowed for recovery from surgery before experiments were performed.

Surgical preparations. After induction with 12 mg/kg of thiopental sodium (Abbott Laboratories, North Chicago, IL), anesthesia was maintained using a mixture of halothane (1%), oxygen (33%), and nitrous oxide (66%). After a maternal abdominal flank incision was performed, the uterus was partially externalized and opened over the fetal hindlimbs. Polyethylene catheters were placed into the fetal femoral arteries and veins bilaterally. A catheter for recording amniotic pressure was also secured to the fetal skin. The left kidney, renal artery, and renal nerves were exposed through a flank incision, and a plastic coated copper wire, used as a ground wire, was secured in the paravertebral muscle. After a branch of the left renal nerve bundle was isolated, platinum electrodes were secured onto the nerve for recording of renal sympathetic nerve activity (RSNA) as described previously (40). Function of the renal nerve was tested by audible monitoring of pulse-synchronous bursts of neural activity and by examining oscilloscope tracings during bolus phenylephrine infusion. When function was demonstrated, electrodes were secured using Sil-Gel (Sil-Gel 604A and 604B, Wacker-Chemie, Munich), and the flank incision was closed in separate layers. After closure of incisions, catheters and wires were exteriorized through subcutaneous tunnels and placed in cloth pouches on the ewe’s flank. Ampicillin sodium (Wyeth Laboratories) was administered to the ewe intramuscularly before surgery (2 g) and infused into the amniotic cavity after surgery (2 g). After surgery, pregnant ewes were returned to individual pens and allowed free access to food and water. One group of ewes received betamethasone (12 mg im) 48 and 24 h before beginning the physiological studies; a second group received no injection. This dose has previously been shown by us to produce increased blood pressure and RSNA after birth (33) and is the dose recommended by the National Institutes of Health Consensus Development Panel for clinical use in pregnant women in preterm labor (19).

Physiological studies. Before the start of the experiments, the ewe was transferred to the laboratory in a small cart that was placed in a Faraday cage. The pregnant ewe was then sedated with diazepam (0.3 mg/kg), given an intravenous bolus infusion of vecuronium bromide (0.1 mg/kg), and intubated and ventilated to maintain venous blood gas values similar to those obtained during spontaneous respiration. Sedation with diazepam and paralysis have previously been shown to have no effect on heart rate (HR), arterial pressure, or plasma catecholamine concentrations in lambs (39). Diazepam (0.1 mg/kg estimated wt) and vecuronium (0.1 mg/kg estimated wt) were also administered to the fetus. Muscle paralysis was necessary to eliminate movements that interfere with nerve recording. Additional doses of vecuronium (0.1 mg/kg) were administered when movement was detected. During the experiments a constant infusion of a solution of 5% dextrose and 0.2% sodium chloride was administered to the ewe at a rate of 125 ml/h and to the fetus at 100 ml·kg⁻¹·day⁻¹. After intubation, a 1-h stabilization period was allowed before the start of the experiment.

During each experiment, fetal mean arterial blood pressure (MABP) and amniotic pressure were recorded continuously using Statham P23Db pressure transducers (Spectramed, Critical Care Division, Oxnard, CA) and a Grass 7–24P chart recorder (Grass Instruments, Quincy, MA). Fetal MABP was corrected relative to concomitant amniotic pressure. HR was monitored with a cardiotachometer triggered from the arterial pressure pulse waves. The renal nerve electrodes and ground wire were attached to a high impedance probe (HIP5, Grass Instruments). The neural signal was amplified (×20,000) and filtered (low-frequency cutoff 100 Hz, high-frequency cutoff 3 kHz) using a Grass Bandpass Amplifier (P511). The output of the amplifier was visually displayed on an oscilloscope (511A, Tektronix, Beaverton, OR), routed to a Grass AM8 audio monitor. The integrated voltage and neurogram signals were displayed on the recorder and simultaneously recorded on line to a personal computer using LABTECH NOTEBOOK (version 7.2; Laboratory Technologies, Wilmington, MA).

Experimental protocol. The experimental protocol is summarized in Fig. 1. After a 1-h equilibration period, fetal values for HR, MABP, and RSNA were obtained by averaging those values over a 10-min period. Arterial blood for determination of blood gases and pH and plasma norepinephrine, epinephrine, cortisol, and ANG II levels was then obtained. The volume of blood sampled from the fetus was replaced immediately with an equivalent volume of maternal blood to avoid any hemodynamic effects of sampling. Baroreflex function in the fetus was then determined by producing ramp changes in MABP with a continuous intravenous infusion of progressive doses of phenylephrine (1–30 μg·kg⁻¹·min⁻¹ over a 2- to 3-min period) using a Harvard infusion pump, while HR was simultaneously recorded. After a 45- to 60-min recovery period for MABP, HR, and RSNA to return to baseline values was allowed, the fetuses exposed to antenatal betamethasone were administered either the AT1 receptor antagonist, losartan (10 mg/kg estimated fetal weight iv; n = 6), or saline vehicle (n = 6). All fetuses not exposed to betamethasone received losartan (n = 6). Functional blockade of AT1 receptors was documented by the absence of a pressor response to ANG II (0.5 μg iv). Sixty minutes later, baseline measurement of MABP, HR, and baroreflex function was again recorded. At the end of this period, the amount of background noise in the fetal nerve signal was assessed by inhibiting nerve activity using an intravenous infusion of the ganglionic blocking agent tetraethylammonium bromide (10 mg/kg).

After the fetal studies were completed, the ewe was returned to the surgical area, and mechanical ventilation continued. Low spinal anesthesia (1% lidocaine, 10 ml) was administered to the ewe, after which the lamb was delivered by cesarean section. Tracheal intubation of the lamb was performed before the umbilical cord was cut. Lambs not...
exposed to betamethasone received exogenous surfactant (survanta 4 ml/kg, kindly provided by Ross Products Division, Abbott Laboratories, Columbus, OH). Lambs were then transferred to the laboratory in a sling-frame assembly to maintain them in an upright position and were mechanically ventilated with a time-cycled, pressure-limited infant ventilator. Initial ventilator settings included FiO2 1.0, a rate of 40 breaths/min, an inspiratory time of 0.4 s, a positive end-expiratory pressure of 4 cm H2O, and a peak inspiratory pressure of 20–26 cm H2O. Arterial blood gases were obtained no less often than every 20 min, and ventilator settings adjusted to maintain partial pressure of O2 in arterial blood (PaO2) at 75–150 mmHg and partial pressure of CO2 (PaCO2) at 40–50 mmHg. Diazepam and vecuronium were administered to the lambs in doses previously noted. At 30, 60, and 120 min after delivery, HR, MABP, and RSNA were recorded for 10 min. Blood for determination of plasma hormone concentrations, and arterial blood gas values during the initial fetal baseline period being defined as 100%.

RESULTS

The effectiveness of AT1 receptor blockade was tested in the fetus and newborn by recording the blood pressure changes in response to ANG II. Losartan attenuated the pressor response to ANG II (0.5 μg iv) from 14 ± 3 to 2 ± 1 mmHg. Although the dose of losartan was not repeated after delivery, effective AT1 receptor antagonism was still present postnatally, because the increase in blood pressure after ANG II was 2 ± 2 mmHg in these animals compared with 19 ± 4 mmHg in animals that did not receive losartan.

Effects of glucocorticoids and AT1 receptor blockade on fetal systemic hemodynamics and RSNA. Antenatal betamethasone administration resulted in significantly higher fetal MABP compared with nonbetamethasone-treated fetuses, whereas no differences were observed for resting HR (Fig. 2). The effect of glucocorticoids on resting fetal RSNA could not be determined by the intact nerve recording techniques used in this study. Losartan had no effect on fetal baseline MABP, HR, or RSNA in either betamethasone-treated or nontreated animals (Figs. 2 and 3).

Effects of AT1 receptor blockade on systemic hemodynamics and RSNA function after delivery. MABP values were significantly increased from fetal values in both groups of betamethasone-treated animals (betamethasone and betamethasone + losartan) 30 and 60 min after delivery but returned to fetal levels by 120 min of age (Figs. 2 and 3). Losartan administration had no effect on this glucocorticoid-facilitated postnatal increase in MABP. In contrast, animals that received losartan alone displayed no immediate postnatal in-
crease in blood pressure, similar to that previously reported in untreated, prematurely delivered lambs (33). No significant differences were detected between fetal or newborn HR values among any treatment group. RSNA significantly increased above fetal values by 60 min after birth and remained elevated at 120 min in betamethasone-treated animals (betamethasone and betamethasone + losartan). Animals that failed to receive betamethasone showed no postnatal increase in RSNA.

**Effects of glucocorticoids and AT1 receptor blockade on baroreflex control of HR.** Antenatal administration of betamethasone significantly attenuated the gain of the fetal HR baroreflex compared with untreated fetuses of similar age (Fig. 4). Fetal administration of losartan had no demonstrable effect on the gain of the fetal HR baroreflex in either betamethasone-treated or nontreated animals. The gain of the HR baroreflex obtained in the newborn was not significantly different from the fetal value in any respective treatment group but remained significantly higher in nonbetamethasone-treated animals. Again, losartan appeared to have no effect on the HR baroreflex in either betamethasone- or nonbetamethasone-treated animals.

**Effect of delivery on arterial blood values.** Fetal and newborn arterial blood values are summarized in Table 1. Arterial PO2, PCO2, and pH were similar among betamethasone-, betamethasone + losartan-, and losartan-treated fetuses during both fetal study periods (P1 and P2). Thirty minutes after birth, significant decreases in pH and increases in PO2 were seen in all three groups of animals. Arterial pH was significantly lower in losartan alone animals at 30, 60, and 120 min after birth compared with betamethasone and betamethasone + losartan animals. No differences in newborn PO2 were seen among the groups, whereas PCO2 was significantly greater at 120 min in losartan animals compared with the other groups.

Fetal plasma cortisol values were significantly less in the two groups that received antenatal betamethasone than in the losartan group (Fig. 5). Plasma cortisol increased after birth in the losartan group but not in the fetuses receiving betamethasone. No differences were detected in fetal ANG II, norepinephrine, or epinephrine values among the three groups (Figs. 5 and 6), although there was a trend for norepinephrine to be higher in the losartan alone groups (P = 0.08). After birth, ANG II levels significantly increased in the be-
tamethasone + losartan and losartan alone animals compared with the respective fetal values and the newborn value for the betamethasone alone lambs. The postnatal circulating catecholamine values were greatest in the losartan alone group.

DISCUSSION

We previously demonstrated in prematurely delivered lambs that the sympathoexcitatory response at birth is significantly attenuated compared with that seen in term fetuses (33). Antenatal administration of glucocorticoids facilitated postnatal cardiovascular and sympathetic adaptations and decreased the sensitivity of the cardiac baroreflex both before and after birth. Because of the well-described effects of glucocorticoids on the vascular reactivity and the importance of the renin-angiotensin system in cardiovascular regulation, we sought to determine the role of endogenous ANG II, and specifically AT1 receptors, on mediating the cardiovascular and autonomic effects of antenatal steroids in prematurely delivered sheep. The results

![Graph](image1)

**Fig. 5.** Plasma angiotensin II (top) and cortisol (bottom) concentrations in betamethasone (open bars), betamethasone + losartan (filled bars), and losartan alone (hatched bars) treated premature sheep before and after delivery by cesarean section. Fetal values obtained before losartan administration. *P < 0.05 compared with fetal value in same group; † P < 0.05 compared with betamethasone (with or without losartan)-treated values at similar time point; # P < 0.05 compared with betamethasone alone treated group at similar time point.

![Graph](image2)

**Fig. 6.** Plasma norepinephrine (top) and epinephrine (bottom) concentrations in betamethasone (open bars), betamethasone + losartan (closed bars), and losartan alone (hatched bars) treated premature sheep before and after delivery by cesarean section. Fetal values obtained before losartan administration. *P < 0.05 compared with fetal value in same group; † P < 0.05 compared with betamethasone (with or without losartan)-treated values at similar time point.
from the present studies confirm our previous findings that antenatal glucocorticoids augment sympathetic responses at birth in premature lambs and attenuate the sensitivity of the cardiac baroreflex both in utero and immediately after birth. In addition, we now find that endogenous ANG II acting on peripherally accessible AT₁ receptors does not mediate facilitation of the postnatal responses of MABP and RSNA in premature lambs by glucocorticoids. Furthermore, endogenous ANG II does not participate in regulating the effects of antenatal glucocorticoids on baroreflex function in preterm fetuses and newborn lambs.

Pharmacological evidence supports the existence of two major subtypes of angiotensin receptors, named type 1 (AT₁) and type 2 (AT₂) (48). The AT₁ receptor appears responsible for mediating the known effects of ANG II on blood pressure, aldosterone secretion, and water and electrolyte balance (5). The role of the AT₂ receptor is poorly understood, although a number of studies suggest a role in apoptosis and tissue remodeling (e.g., Ref. 11). In the current study, we speculated that the prenatal and immediate postnatal hemodynamic effects of antenatal glucocorticoid administration were mediated, at least in part, by increased activity of the renin-angiotensin system. In support of this hypothesis, glucocorticoid responsive elements have been identified in the 5’-flanking regions of the renin, angiotensinogen, and AT₁ receptor genes (7, 16).

In vivo and in vitro studies have shown that glucocorticoids stimulate accumulation of AT₁ mRNA and binding sites in vascular smooth muscle (13, 26, 31). Inhibition of the renin-angiotensin system at parturition attenuates the normal increase in blood pressure at birth in full-term lambs and alters postnatal baroreflex function, whereas peripheral or central AT₁ receptor blockade lowers blood pressure and resets baroreflex control of HR and RSNA toward lower pressure in 3- to 7-day-old lambs (35, 36).

Increases in peripheral vascular resistance and cardiac output may contribute to the increase in fetal arterial blood pressure during glucocorticoid administration or the increased postnatal blood pressure after antenatal exposure to glucocorticoids (6). Studies using synthetic glucocorticoids, such as dexamethasone or betamethasone, suggest that the increased blood pressure is independent of mineralocorticoid-mediated effects, such as sodium retention or volume expansion (14). Rather, it appears that glucocorticoids directly alter vascular responsiveness to circulating vasoactive agents. Studies in adult vasculature have shown that glucocorticoids increase vascular responsiveness to norepinephrine and ANG II, whereas in the fetal sheep, cortisol administration enhances vascular reactivity to ANG II but not norepinephrine (14, 45). Infusion of betamethasone or dexamethasone to achieve plasma values similar to those seen in infants after antenatal glucocorticoid administration results in a significant increase in femoral vascular resistance (6).

Small resistance branches of the fetal femoral artery vessels exposed to betamethasone in vivo demonstrate marked abnormalities in function, including an enhanced in vitro responsiveness to a depolarizing potassium solution and reduced relaxation to vasodilators, although the contractile responses to norepinephrine are unchanged (2). Thus betamethasone may directly alter excitation contraction coupling in vascular smooth muscle, as suggested by Anwar et al. (2) by altering voltage-gated calcium channels or downregulating sodium-calcium exchanger activity. Altered regulation of α- and β-adrenergic receptor density and coupling to or functional activity of signal transduction mechanisms have also been proposed to mediate the increased cardiovascular responses in glucocorticoid-treated fetuses (22, 41, 42, 47). Glucocorticoids may also regulate the synthesis of vasoactive compounds, such as prostaglandins or nitric oxide, which in turn modulate peripheral vascular reactivity. Recently, Wallerath et al. (50) demonstrated that expression of endothelial nitric oxide synthase is downregulated in adult rats with dexamethasone-induced hypertension. Dexamethasone treatment destabilized endothelial nitric oxide synthase mRNA and reduced gene transcription. Whether similar effects of glucocorticoids occur in the fetal environment to increase blood pressure requires further investigation.

Although we anticipated that administration of losartan to block peripheral AT₁ receptors to fetuses administered betamethasone would decrease both fetal and postnatal MABP, the absence of this effect would suggest that the increase in fetal and newborn blood pressure observed after antenatal glucocorticoid exposure is not mediated by increased vascular responsiveness to endogenous ANG II. This lack of effect was likely not a result of incomplete AT₁ receptor blockade, because the dose of losartan used inhibited the pressor response to exogenous ANG II administered to both the fetus and newborn and has previously been shown by us to acutely reduce blood pressure in older fetuses and newborn sheep and reset the cardiac baroreflex toward lower pressure (19, 36, 37). Stevenson et al. (19) also reported in fetal sheep at 125–132 days of gestation that losartan (10 mg/kg iv) reduced the fetal systolic pressure response to an intravenous infusion of 5 ug of ANG II from ~27 to 7 and 6 mmHg, respectively, 1 and 2 h after administration. Repeating the dose of losartan after 1 h did not further attenuate the pressor response to ANG II. In these same animals, fetal MABP decreased by slightly <7 mmHg, this maximum effect being reached within 1 h. In the present study, the fetuses were of a younger gestational age (118–123 days), and it is possible that endogenous ANG II contributes less to the maintenance of MABP in this younger age group. Of note, the absence of a depressor response is in contrast to a previous study by Samyn et al. (29) performed in 110-day fetuses in which a 48-h constant infusion of losartan (25 mg·kg⁻¹·day⁻¹) produced a significant decrease in blood pressure. The decrease in blood pressure in this 110-day group was not present during the initial 12 h of the study (unpublished observation) but was present at 24 and 48 h, suggesting the mechanisms of the depressor effect of losartan may be different at this developmental stage.
Because losartan appears to cross the blood-brain barrier and blood-brain barrier permeability is increased in young fetuses, blockade of central AT$_1$ receptors, which are present in numerous central cardiovascular regulatory centers, may contribute to the decrease in blood pressure after prolonged exposure to losartan (18, 43).

We did not measure cardiac output and thus cannot rule out the possibility that losartan produced a decrease in peripheral vascular resistance and that MABP was maintained by a concurrent increase in cardiac output. However, given the absence of an increase in HR after losartan administration and the limited ability of the newborn heart to increase stroke volume beyond the normal increase that occurs at birth (1), we believe this to be unlikely. Therefore, glucocorticoid-mediated increases in peripheral vascular resistance must occur by mechanisms other than stimulation of vascular AT$_1$ receptors. One such mechanism would include increased neurogenic tone resulting from increased peripheral sympathetic activity or altered release/reuptake of norepinephrine at the presynaptic nerve ending or terminal. Unfortunately, our present method for recording sympathetic nerve activity does not allow us to determine if glucocorticoids altered fetal sympathetic tone. On the other hand, the increase in postnatal sympathetic activity in glucocorticoid-treated compared with control animals may certainly contribute to the increased MABP seen in these lambs.

Results of this study confirm our previous finding that antenatal glucocorticoid administration results in enhanced postnatal sympathetic activity in prematurely delivered lambs. The mechanisms for this response are not known and have been speculated on in our previous study (33). ANG II has been shown in a number of species to regulate sympathetic activity and baroreflex function (24, 27). These effects are mediated by circulating ANG II acting on circumventricular organs as well as locally produced ANG II within central cardiovascular centers, including the rostral ventrolateral medulla (3, 25, 44). Although little is known regarding the function of endogenous ANG II in the brain during early development, we have previously shown that intracerebroventricular administration of losartan in newborn lambs decreases arterial pressure and resets the HR and RSNA baroreflexes to lower pressures (36). Thus there are reasons to believe that ANG II may be important in regulating cardiovascular function sympathetic tone during fetal life and during the transition to the extraterine environment. The finding that peripheral administration of losartan had no effect on resting fetal RSNA, the change in RSNA accompanying birth, or the HR baroreflex suggests that endogenous ANG II stimulation of AT$_1$ receptors that are accessible to losartan within the time frame of this study participates little in regulating basal cardiovascular function at this stage of development. However, the contribution of central AT$_1$ receptors to the alterations in physiological responses mediated by antenatal glucocorticoids cannot be determined. Knowledge regarding the degree of central AT$_1$ receptor inhibition, which likely depends on the time course and concentration dependence of losartan crossing the blood-brain barrier, would be necessary for this assessment.

Serum cortisol values were low in betamethasone-treated fetuses and failed to increase after birth, consistent with inhibition of the hypothalamic-pituitary-adrenal axis by glucocorticoids. Fetuses administered losartan alone demonstrated serum cortisol levels comparable to those reported in fetuses of similar gestational ages (33). After delivery, cortisol levels significantly increased, again consistent with findings previously reported (33). Although fetal serum ANG II levels were similar among groups, ANG II levels significantly increased after birth in animals treated with losartan alone and in combination with betamethasone. This increase likely resulted from AT$_1$ receptor blockade and the loss of feedback inhibition by circulating ANG II on renin and subsequent ANG II production.

The levels of circulating norepinephrine and epinephrine were significantly greater after birth in all three groups of animals; however, the postnatal increases in catecholamines were larger in the losartan alone treated animals compared with the groups that received antenatal betamethasone. Other investigators have observed premature lambs to have greater catecholamine responses at birth than term, whereas premature fetuses exposed to antenatal glucocorticoids have attenuated postnatal increases in catecholamines (23, 42). Reasons for this finding are not known but are likely related to glucocorticoid-induced alterations in the balance of neurogenic and nonneurogenic control mechanisms of catecholamine release from the fetal adrenal gland (38).

Perspectives

There is increasing interest regarding the nonpulmonary effects of glucocorticoid exposure to the fetus. Maternal glucocorticoid administration improves cardiovascular function after birth and lessens the incidence of complications associated with prematurity. However, a number of studies have indicated prenatal glucocorticoid exposure may lead to permanent effects on vascular, hormonal, and central regulatory mechanisms involved in maintaining cardiovascular homeostasis, so called “fetal programming” (20, 32). The present study provides novel information regarding the mechanism of glucocorticoid-induced increases in fetal and postnatal blood pressure. Continued investigation on the effects of these steroids of fetal and postnatal development is essential if we are to better understand both immediate and long-term consequences of antenatal glucocorticoid treatment.

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