Antenatal glucocorticoids alter premature newborn lamb neuroendocrine and endocrine responses to hypoxia

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Antenatal glucocorticoids alter premature newborn lamb neuroendocrine and endocrine responses to hypoxia. Am J Physiol Regulatory Integrative Comp Physiol 279: R830–R838, 2000.—Glucocorticoids are administered for preterm labor to improve postnatal adaptation. We assessed the effect of antenatal betamethasone (Beta) treatment on preterm newborn lamb neuroendocrine [catecholamine, arginine vasopressin (AVP)] and endocrine [triiodothyronine (T3), ANG II, and atrial natriuretic factor (ANF)] adaptive responses following delivery and a hypoxic challenge. Beta treatment included direct fetal injection at 0.2 (F0.2; n = 8) or 0.5 (F0.5; n = 7) mg/kg estimated fetal body weight or maternal injection with 0.2 (n = 8) or 0.5 mg/kg (M0.5; n = 8). Control animals received fetal and maternal intramuscular injections of saline (n = 8). After 24 h, lambs were delivered by cesarean section, surfactant treated, and ventilated for 4 h. Relative to the control lambs, 3 h after delivery, there was a marked suppression of plasma cortisol, epinephrine, norepinephrine, and ANG II levels and elevated plasma T3 and ANF levels, systolic blood pressure, and left ventricular contractility (dP/dt; F0.5 and M0.5) values in F0.5 and both maternal Beta-treated groups. However, Beta treatment augmented the cardiac output, cortisol, norepinephrine, AVP, and ANF responses to 20 min of hypoxia (PO2 = 25–30 mmHg). We concluded that short-term (24 h) antenatal glucocorticoid exposure 1) alters preterm newborn postnatal blood pressure regulation in the face of marked depression of plasma cortisol, catecholamine, and ANG II levels and 2) augments the postnatal neuroendocrine and endocrine responses to a hypoxic challenge.

catecholamines; arginine vasopressin; atrial natriuretic factor; betamethasone; cardiovascular

METHODS

Animal protocols were reviewed and approved by the Harbor-UCLA Animal Care and Use Review Committee. Pregnant ewes with singleton fetuses (n = 39) at 126 or 127 days gestational age were randomized into one of four betamethasone treatment groups or a saline-treated group (control). All ewes and fetuses received fetal and maternal injections with saline or betamethasone. Control animals received two (fetal injections of saline and betamethasone were given to the intact ewe. On day 90 of gestation, the ewes were anesthetized, and the fetal lambs underwent brief hypoxia (PO2 = 50 mmHg) for 10 min, followed by resumption of normoxia. The ewes were then delivered by cesarean section, and the lambs were ventilated. The ewes were allowed to deliver the remaining lambs without further intervention. All newborn lambs were ventilated for 4 h. Relative to the control lambs, 3 h after delivery, there was a marked suppression of plasma cortisol, epinephrine, norepinephrine, and ANG II levels and elevated plasma T3 and ANF levels, systolic blood pressure, and left ventricular contractility (dP/dt; F0.5 and M0.5) values in F0.5 and both maternal Beta-treated groups. However, Beta treatment augmented the cardiac output, cortisol, norepinephrine, AVP, and ANF responses to 20 min of hypoxia (PO2 = 25–30 mmHg). We concluded that short-term (24 h) antenatal glucocorticoid exposure alters preterm newborn postnatal cardiovascular and neuroendocrine adaptations at birth. In addition, preterm newborn lambs were challenged with a brief period of hypoxia before their delivery to assess the impact of antenatal glucocorticoid exposure on postnatal cardiovascular, neuroendocrine, and endocrine system responsiveness.

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PRETERM NEWBORN ENDOCRINE RESPONSES TO HYPOXIA

and maternal) saline injections. On the basis of an estimated fetal weight of 2.5 kg, fetuses received ultrasound-guided intramuscular injections of saline or betamethasone (Celestone Soluspan; Schering Pharmaceutical, Kenilworth, NJ) at 0.2 (F0.2; n = 8) or 0.5 (F0.5; n = 7) mg/kg as previously detailed (14). Maternal betamethasone treatments included 0.2 (M0.2; n = 8) or 0.5 (M0.5; n = 8) mg/kg. The 0.2 and 0.5 mg/kg fetal doses were selected based on our previous experience with fetal therapy (38). The M0.2 dose was chosen to mimic the 12-mg total betamethasone dose used clinically and previously demonstrated to induce fetal lung maturation in sheep (23). The M0.5 dose was selected to match the high-dose fetal treatment. The postnatal pulmonary and renal responses for some of these animals were reported elsewhere (2, 33). The focus of this report is the effect of antenatal glucocorticoid exposure on the preterm newborn postnatal neuroendocrine and endocrine system adaptations and the responses to the stress of hypoxia.

Ewes were sedated 24 h after treatments with 15–20 mg/kg im ketamine (Ketaject; Phoenix Pharmaceutical, St. Joseph, MO) and given combined spinal-epidural anesthesia with 10 ml of 2% lidocaine/0.5% bupivacaine (1:1). The fetal head and neck were exposed through a small hysterotomy. The fetus was sedated with a ketamine (10 mg/kg im) and acepromazine (0.2 mg/kg im; PromAce7; Ayerst Laboratories, New York, NY) mixture administered on the basis of estimated fetal body weight. Although possible adverse effects of sedation cannot be excluded, this ketamine/acepromazine mixture has been used extensively without apparent detrimental effects on preterm newborn blood pressure, heart rate, and cardiac output (2, 9, 29, 33). The anterior neck was infiltrated with 2% lidocaine, an endotracheal tube was secured by tracheotomy, and lung liquid was aspirated. After delivery, lambs were towel dried, weighed, and treated with 100 mg/kg surfactant (Survanta7; Ross Laboratories; Columbus, OH) via direct intratracheal instillation. Lambs were mechanically ventilated with pressure-limited infant ventilators (Sechrist, Anaheim, CA) set to deliver 100% O2. Initial ventilator settings were a positive end expiratory pressure of 3 cmH2O, a rate of 40 breaths/min, and an inspiratory time of 0.7 s. Only peak inspiratory pressure (PIP) was adjusted to maintain Pco2 values of 40–50 mmHg. PIP was limited to 35 cmH2O to avoid pneumothorax. After delivery of the lamb, blood was collected from the ewe into sterile transfusion bags containing anticoagulant (sodium citrate) for replacement of newborn blood samples.

The investigators delivering and managing the preterm lambs were blinded as to treatment groups. On stabilization of ventilation (1–2 min after birth), a catheter was placed in the descending aorta via the umbilical artery for blood sampling and blood pressure monitoring. Because we have found that initial volume administration improves overall cardiovascular stability in the premature lamb model, all lambs received a volume load of heparinized placental blood (10 ml/kg) within 5 min of delivery. Blood pressure and heart rate were monitored continuously. The skin was infiltrated with lidocaine, the right carotid artery was isolated, and a vascular catheter was inserted with lidocaine, the right carotid artery was isolated, and a vascular catheter was maintained by con-
Values are means ± SE; n, no. of animals. *Differs from control value; all hypoxia PO₂ values were significantly below the prehypoxia values.

Table 1. Arterial blood gas and pH values in preterm newborn lambs

<table>
<thead>
<tr>
<th>Betamethasone, mg/kg</th>
<th>Control</th>
<th>Fetal 0.2</th>
<th>Fetal 0.5</th>
<th>Maternal 0.2</th>
<th>Maternal 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>PO₂, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord</td>
<td>47 ± 2</td>
<td>46 ± 2</td>
<td>44 ± 2</td>
<td>42 ± 1</td>
<td>43 ± 2</td>
</tr>
<tr>
<td>Prehypoxia</td>
<td>47 ± 2</td>
<td>48 ± 2</td>
<td>43 ± 3</td>
<td>47 ± 2</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>49 ± 2</td>
<td>46 ± 3</td>
<td>43 ± 3</td>
<td>45 ± 2</td>
<td>41 ± 3</td>
</tr>
<tr>
<td>Recovery</td>
<td>50 ± 3</td>
<td>46 ± 1</td>
<td>44 ± 3</td>
<td>50 ± 3</td>
<td>47 ± 3</td>
</tr>
<tr>
<td>PO₂, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord</td>
<td>27 ± 2</td>
<td>32 ± 2</td>
<td>29 ± 1</td>
<td>32 ± 2</td>
<td>30 ± 1</td>
</tr>
<tr>
<td>Prehypoxia</td>
<td>170 ± 25</td>
<td>163 ± 43</td>
<td>328 ± 44*</td>
<td>315 ± 25*</td>
<td>289 ± 38*</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>27 ± 4</td>
<td>26 ± 3</td>
<td>29 ± 2</td>
<td>32 ± 6</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>Recovery</td>
<td>134 ± 22</td>
<td>194 ± 35</td>
<td>331 ± 39*</td>
<td>291 ± 36*</td>
<td>308 ± 49*</td>
</tr>
<tr>
<td>pH</td>
<td>7.33 ± 0.01</td>
<td>7.35 ± 0.01</td>
<td>7.37 ± 0.01*</td>
<td>7.37 ± 0.01*</td>
<td>7.37 ± 0.01*</td>
</tr>
<tr>
<td>Prehypoxia</td>
<td>7.28 ± 0.02</td>
<td>7.29 ± 0.02</td>
<td>7.35 ± 0.02*</td>
<td>7.33 ± 0.01</td>
<td>7.35 ± 0.02*</td>
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<tr>
<td>Hypoxia</td>
<td>7.29 ± 0.02</td>
<td>7.30 ± 0.03</td>
<td>7.35 ± 0.02</td>
<td>7.35 ± 0.02</td>
<td>7.37 ± 0.03</td>
</tr>
<tr>
<td>Recovery</td>
<td>7.27 ± 0.02</td>
<td>7.30 ± 0.02</td>
<td>7.32 ± 0.03</td>
<td>7.28 ± 0.03</td>
<td>7.30 ± 0.02</td>
</tr>
</tbody>
</table>

Results

Umbilical artery blood gas and pH values were in the normal range and were similar for all groups at delivery except for significantly higher arterial pH values in the F₀.5, M₀.2, and M₀.5 groups relative to the control group. Arterial blood gas and pH values before (prehypoxia) and after the onset of hypoxia and 1 h after initiation of hypoxia (recovery) are summarized in Table 1. There were no changes in PO₂ with time or among the groups at any time. Prehypoxia arterial PO₂ values were similar in the control and F₀.2 groups. However, arterial PO₂ values were significantly higher in the other groups of animals treated with antenatal glucocorticoids regardless of route of administration or dose. Similar degrees of hypoxia were achieved in all groups treated with betamethasone relative to the control group and were significantly suppressed in the F₀.5 and M₀.2 groups relative to control lambs (Fig. 2). Plasma cortisol levels in control lambs significantly increased postnatally (prehypoxia) relative to the umbilical cord values. Although plasma cortisol levels increased postnatally in the F₀.2 and M₀.2 animals, the levels achieved were more than twofold below the control prehypoxia values. Plasma cortisol levels did not increase postnatally in the high-betamethasone dose (F₀.5 or M₀.5) groups, and the prehypoxia cortisol levels in the betamethasone-treated groups were significantly reduced relative to the control values. Hypoxia significantly increased plasma cortisol levels in both the M₀.2 and M₀.5 groups, whereas hypoxia had no effect on plasma cortisol levels in the control, F₀.2, and F₀.5 groups. Peak plasma cortisol levels during hypoxia were reduced in all betamethasone-treated groups relative to the control group (Fig. 2).
Umbilical cord plasma T₃ levels were significantly elevated in all betamethasone-treated groups relative to the control group (Fig. 2). Mean plasma T₃ levels increased in all groups postnatally. Prehypoxia plasma T₃ levels in all betamethasone-treated groups were at least twofold above the control group values. However, plasma T₃ levels did not change in any group in response to hypoxia. Whereas the umbilical cord plasma T₃ levels tended to be lower in the maternal betamethasone-treated groups relative to the control value of 11.3 ± 0.5 ng/ml, there were no changes in plasma T₄ values in any group in response to hypoxia (data not shown).

The umbilical cord plasma epinephrine values tended to be lower in the lambs exposed to antenatal betamethasone. However, the level of suppression was statistically significant only in the M₀.₅ group. Control lamb plasma epinephrine levels significantly increased to ~1,500 pg/ml postnatally (prehypoxia). In contrast, plasma epinephrine levels were suppressed in the F₀.₂ and both maternal betamethasone-treated groups before hypoxia (Fig. 3). Plasma epinephrine levels did not change in response to hypoxia, except in the M₀.₂
group. Although mean plasma epinephrine levels achieved in response to hypoxia in the betamethasone-treated groups were, at most, only 40% (F0.5) of the control group hypoxia values, the degree of suppression was statistically significant only in the M0.5 group.

Umbilical cord plasma norepinephrine levels were not different among the groups (Fig. 3). Although mean plasma norepinephrine levels increased more than twofold postnatally in the control lambs, the change was not statistically significant. In contrast, postnatal plasma norepinephrine levels were significantly suppressed in the F0.5, M0.2, and M0.5 groups relative to the control values. Plasma norepinephrine levels did not change in response to hypoxia in the control group but significantly increased in all betamethasone-treated groups (Fig. 3). However, the peak hypoxia-induced plasma norepinephrine values achieved were not different between the control and betamethasone-treated groups.

The umbilical cord plasma AVP levels did not differ significantly among the groups, although plasma AVP levels were twofold lower in the F0.5 and both maternal betamethasone-treated groups. Plasma AVP levels increased postnatally in the M0.2 group but did not differ among the groups before initiation of hypoxia (Fig. 4). Whereas plasma AVP levels did not change in the control and F0.2 groups in response to hypoxia, plasma AVP levels increased three- to fivefold in the remaining betamethasone-treated groups. In contrast to the catecholamine and AVP responses, umbilical cord plasma ANF levels were significantly increased in the F0.5, M0.2, and M0.5 groups. Plasma ANF levels did not change in any group postnatally, although plasma ANF levels in the F0.2 and M0.5 groups were significantly elevated relative to the control group hypoxia values. Plasma ANF levels increased significantly in all groups in response to hypoxia. The change in plasma ANF levels in the betamethasone-treated groups was, on average, larger than in the control lambs, and the increase was significantly larger in the M0.2 and M0.5 groups.

Although there was a more than twofold suppression of umbilical cord plasma ANG II levels in all betamethasone-treated groups, the suppression was not statistically significant. (Fig. 4). However, prehypoxia plasma ANG II levels were significantly suppressed in the F0.5 and both maternal betamethasone-treated lambs relative to the control group. Plasma ANG II levels did not change in any group in response to hypoxia, and plasma ANG II levels in the F0.5 and M0.2 groups were significantly reduced relative to the control values during hypoxia.

**DISCUSSION**

The transition from fetal to newborn life is associated with marked changes in function of the major organ systems. Our prior studies examining the effects of antenatal glucocorticoid exposure on postnatal physiological adaptation in sheep have demonstrated improvements in pulmonary, cardiovascular, metabolic, and renal adaptation at birth (2, 9, 29, 31, 37, 38). However, we have also observed glucocorticoid-related reductions in the circulating levels of multiple neuroendocrine and endocrine systems thought to be critical to neonatal adaptation. Thus it was unclear whether these alterations in circulating hormone levels represented inhibition of secretion and/or an inability to respond to the physiological stress associated with premature delivery.

In the present studies, we delivered control and betamethasone-treated preterm lambs, monitored their physiological adjustments over 3 h postnatally, and tested neuroendocrine and endocrine responsiveness to hypoxia. The studies included groups given glucocorticoids by direct fetal injection, a paradigm we have extensively investigated (2, 9, 14, 29, 31, 33). Other groups received a maternal betamethasone dose equivalent to the dose used clinically (M0.2) and a higher maternal dose chosen to achieve fetal plasma betamethasone levels similar to the lower direct fetal dose (2). Our results demonstrate that, in general, single antenatal glucocorticoid treatment within 24 h of preterm delivery suppresses postnatal circulating cortisol, catecholamine, AVP, and ANG II levels and increases circulating levels of T3 and ANF. Irrespective of these endocrine effects, betamethasone treatment
also resulted in postnatal increases in systolic blood pressure and left ventricular dP/dt. Moreover, antenatal glucocorticoid exposure attenuated the expected epinephrine response to hypoxia while augmenting the norepinephrine, AVP, and ANF responses. Overall, responses to glucocorticoid exposure were independent of the route of administration (fetal vs. maternal), and the magnitude of the endocrine responses to fetal glucocorticoid treatment was clearly dose related.

Despite no differences in heart rate or cardiac output, the F0.5 and both maternal betamethasone-treatment groups had higher systolic blood pressures relative to the control lambs. Thus the higher systolic blood pressure primarily reflects an increase in systemic vascular resistance (7). Elevations in fetal plasma glucocorticoid levels via a number of differing treatment paradigms increase resting fetal and preterm newborn mean arterial blood pressures (29, 38, 39), and Derks et al. (7) reported an association between glucocorticoid-induced increases in fetal blood pressure and an increase in femoral vascular resistance. Sustained elevation (24 h or more) in newborn mean arterial blood pressures after glucocorticoid exposure have now been reported from premature newborn sheep (29), baboons (11), and humans (15).

The available data indicate that glucocorticoid-induced increases in blood pressure are solely attributable to glucocorticoid receptors and not mineralocorticoid receptors (7). Because this phenomenon is gestation dependent in sheep, i.e., blood pressure effects are absent after 130 days gestation (39), augmented autonomic nervous system maturation may be a critical component in the overall cardiovascular response to antenatal glucocorticoid administration. Although the dP/dt measurements provide only a crude index of cardiac function, the parallels between systolic blood pressure and peak left ventricular pressure and the increases in left ventricular dP/dt are consistent with glucocorticoid-related increases in overall cardiac contractility (29). This latter effect appears to be related to augmented adrenergic receptor-dependent myocardial cyclic AMP production (38) and not increased receptor density in the heart. In addition, the elevated plasma T3 levels observed in the betamethasone-treated lambs may have contributed to the overall improved myocardial function in these animals.

Despite the increase in resting blood pressure and a pattern of overall advanced maturation, the cardiovascular responses to hypoxia were inconsistent and limited to a small increase in blood pressure in the F0.2 group and increases in cardiac output in both fetal treatment groups. These minimal responses are in marked contrast to the pronounced responses of the chronically catheterized fetal lamb to periods of hypoxia (13). One explanation is the absence of changes in arterial blood Pco2 and/or pH may have limited the cardiovascular responses (32). Alternatively, the degree of hypoxia achieved may not have been sufficient to elicit some of the cardiovascular responses. Although an arterial Po2 value of 25 mmHg is clearly in the hypoxic range for a lamb or adult ewe, this Po2 level is at the upper range of normal fetal arterial Po2 values. This suggests that resetting of the chemoreceptor threshold from a fetal level to a higher adult level had not occurred by 3 h postnatally. Whether this resetting is related to peripheral chemoreceptor function cannot be assessed from the present experiments. However, robust hypoxia-induced AVP and ANF responses in the absence of cardiovascular effects is a response pattern consistent with the view that central oxygen-sensitive site(s) may develop before peripheral chemoreceptor activation in the fetus (17).

Our laboratory and others have reported exponential increases in the plasma levels of a number of vasoactive mediators at birth (24, 30), including increases in circulating epinephrine, norepinephrine, and AVP. The increase in circulating levels of both epinephrine and norepinephrine are significantly greater in preterm than in full-term animals (30). Because fetal chemical sympathectomy significantly obviates postnatal increases in circulating norepinephrine (1) and fetal adrenalectomy completely abolishes the postnatal increase in circulating epinephrine, circulating norepinephrine responses reflect neuronal spillover, whereas epinephrine release represents adrenal medullary function. Although norepinephrine depletion from the fetal circulation is without effect on overall physiological adaptive potential (1), adrenalectomy markedly impairs cardiovascular, pulmonary, and metabolic adaptation in the immediate postnatal period (27). Thus even though an increase in circulating epinephrine at birth is thought to be important to many of the major physiological adaptations (27, 30), antenatal betamethasone treatment was associated with overall improvements in cardiovascular and pulmonary function (33) in the face of a marked suppression of circulating catecholamine levels. A similar attenuation of circulating catecholamine levels concomitant with increased blood pressure has been reported in fetal sheep during infusion of cortisol (43) and betamethasone/dexamethasone (7).

Glucocorticoid administration increases fetal arterial blood pressure (7), decreases fetal and newborn plasma catecholamine and ACTH stress responses (18, 26, 34), and decreases central sympathoadrenal activity in adult rats (19, 41). This latter effect has been documented by both microdialysis studies (41) and by examination of changes in regional neurotransmitter content as an index of nervous system activity (19). Because the betamethasone-treated animals had attenuated postnatal catecholamine responses, antenatal glucocorticoids may act by inhibiting or attenuating baroreceptor- and/or vestibular-mediated central sympathetic outflow. Whether this effect is related to an apparent resetting of baroreflex-mediated blood pressure regulation in the betamethasone-treated lambs is not clear. Other investigators have proposed that regulation of sympathoadrenal and hypothalamo-pituitary-adrenal system activity is colocalized and coregulated coordinately via central mechanisms (18, 26).

Plasma catecholamine, ACTH, and cortisol levels increase after adrenalectomy, and the response of each of
these systems to an immobilization stress is augmented (26).

The betamethasone-induced suppression of plasma cortisol and ANG II levels and the more than 50% reduction in plasma AVP levels in the F₀.₅ and both maternal betamethasone-treated groups are consistent with the acute effects of cortisol infusion on these systems. Although plasma ACTH levels were not assessed in the current studies, it appears likely the betamethasone-induced suppression of preterm newborn plasma cortisol levels reflects feedback inhibition to suppress ACTH release. Whereas the exact mechanism for betamethasone-related reductions in plasma AVP levels is not known, baroreflex-related attenuation of AVP release due to the higher fetal blood pressures and the dense accumulation of glucocorticoid receptors in the anterior hypothalamus adjacent to AVP regulatory neurons may be important contributing factors (21).

Glucocorticoid administration also was associated with marked attenuation of the renin-angiotensin system (Fig. 4). The suppression of circulating ANG II levels can be explained by glucocorticoid-induced suppression of both renal renin gene expression (36) and plasma renin activity (44) and hepatic angiotensinogen gene expression (3, 25). A betamethasone-mediated suppression of the renin-angiotensin system is surprising from the perspective that, due to nervous system immaturity, circulating ANG II is a critical determinant of preterm fetal peripheral vasoconstriction and blood pressure and overall blood pressure regulation. For example, administration of the ANG II antagonist saralasin or the angiotensinogen-converting enzyme inhibitor captopril decreases resting blood pressure to a much greater extent in preterm than in near-term fetal lambs (20). This apparent discrepancy may be partially explained by glucocorticoid-induced increases in vascular ANG II AT₁-receptor expression and increased vascular responsiveness to ANG II (35, 39). These effects, in combination with glucocorticoid-induced autonomic nervous system maturation, discussed above, may be important aspects of the overall glucocorticoid-induced effect to increase fetal blood pressure.

The augmented ANF response to hypoxia in the present study was unexpected. Whereas hypoxia has been shown to be a potent stimulus for ovine fetal ANF secretion (13), ANF responsiveness is typically thought to be inversely related to advancing gestational age (5). Basal fetal plasma ANF levels are typically high and decrease with advancing gestation. If glucocorticoids induce fetal maturation, we would have expected umbilical cord ANF levels to be suppressed in the betamethasone-treated animals, which was not the case (Fig. 4). Alternatively, the glucocorticoid-induced increase in blood pressure and vascular resistance may have increased venous return and/or right atrial pressure sufficiently to increase plasma ANF levels (5). Because cardiac cell ANF release is at least partially dependent on both α- and β-adrenergic receptor mechanisms, a glucocorticoid-induced increase in β-adrenergic receptor effector system coupling (38, 40) may have contributed to the augmented ANF response observed in the betamethasone-treated lambs.

There are several potentially important clinical implications of these studies. Clinical epidemiologic and demographic studies have consistently demonstrated that antenatal glucocorticoid exposure of the human fetus significantly reduces mortality in the premature newborn (6). We and others have suggested this effect is due not only to accelerated pulmonary maturation, but improvement in physiological, cardiovascular, metabolic, and endocrine changes at birth (28). The present studies confirm and extend these observations by providing direct evidence that antenatal glucocorticoids do not impair the physiological responses to postnatal stressful events such as hypoxia. Thus glucocorticoids attenuated the circulating levels of a variety of vasoactive agents (catecholamines, AVP, and ANG II), whereas pulmonary function, blood pressure, cardiac output, and metabolic activity were all maintained, and the critical physiological responses to a stressful postnatal event (hypoxia) were not impaired.

**Perspectives**

Antenatal glucocorticoid administration has gained wide acceptance as an effective therapeutic approach to reducing postnatal morbidity and mortality due to lung immaturity in premature human infants. However, as clearly demonstrated by the present and previous studies, glucocorticoid-related effects on the preterm newborn are not limited to the lungs. In fact, glucocorticoid-induced cardiovascular effects appear to contribute to improved perinatal blood pressure regulation in the premature human newborn (22). Whereas these collective beneficial effects have important clinical applications, concerns also have been raised. For example, emerging data from a variety of sources suggest that antenatal glucocorticoid administration may predispose the individual to vascular hypertension later in life (8). It is therefore essential that future research focus on distinguishing the basic mechanisms for glucocorticoid-induced pulmonary versus cardiovascular effects so that more specific therapeutic agents might be developed or identified.

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