Early gestation dexamethasone alters baroreflex and vascular responses in newborn lambs before hypertension

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Submitted 19 September 2005; accepted in final form 19 February 2006

Dexamethasone administered to pregnant ewes by intravenous infusion over 48 h before 27 days gestation (term 145 days) and lambs were allowed to deliver (n = 6 in each group). Resting mean arterial blood pressure (MABP; 77 ± 1 vs. 74 ± 3 mmHg) and heart rate (HR; 249 ± 9 vs. 226 ± 21 beats/min) were similar in Dex-exposed and control animals, respectively. The arterial baroreflex function, relating changes in HR to MABP, was significantly shifted toward higher pressure in the Dex-exposed lambs although no change in the sensitivity (gain) of the response was seen. In vivo changes in blood pressure in response to bolus doses of ANG II (20, 50, and 100 ng/kg) and phenylephrine (2, 5, and 10 µg/kg) were similar in the two groups. However, Dex lambs displayed greater decreases in MABP in response to ganglionic blockade with tetraethylammonium bromide (10 mg/kg; -30 ± 3 vs. -20 ± 3 mmHg, P < 0.05) and greater increases in MABP after nitric oxide synthase blockade with Nω-nitro-l-arginine (25 mg/kg; 23 ± 3 vs. 13 ± 2 mmHg, P < 0.05) compared with control lambs. By in vitro wire myography, mesenteric and femoral artery microvessel contractile responses to KCl were similar, whereas responses to endothelin (in mesenteric) and norepinephrine (in femoral) were significantly attenuated in Dex lambs compared with controls. Femoral vasodilatory responses to forskolin and sodium nitroprusside were similar in the two groups (n = 4). These findings suggest that resetting of the baroreflex, accompanied by increased sympathetic activity and altered nitric oxide-mediated compensatory vasodilatory function, may be important contributors to programming of hypertension.

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pertension may be masked by compensatory increases in endothelial nitric oxide production early in life.

METHODS

Animals and Surgical Preparations

Time-dated pregnant ewes of Dorset and Suffolk mixed breeding were obtained from Iowa State University (ISU) and housed at the ISU Agricultural Station throughout the course of study. At 27–28 days gestation (term being ~145 days), a 16-gauge, single-lumen polyethylene catheter (Cook Critical Care, Bloomington, IN) was placed in the left jugular vein of the pregnant ewe by using a modified Seldinger technique, and dexamethasone (0.28 mg·kg⁻¹·day⁻¹; Gen- sia Sicor Pharmaceuticals, Irvine, CA) or an equivalent volume of vehicle (0.9% NaCl) was continuously infused over 48 h. The catheter was then removed, and the ewes were allowed to complete gestation. The ewes delivered naturally with two twin and four single deliveries within both the dexamethasone-exposed group and the control group. A single lamb from each twin group was used for the studies; thus, a total of six lambs of either sex was included in each group. Before the infusion period, pregnant ewes were allowed to pasture graze and were provided with 1 pound/day of shelled corn with a mineral supplement. After the infusion period, ewes were fed an alfalfa/grass mixture diet along with 1–3 pounds/day of shelled corn with mineral and protein supplementation. Lambs were allowed to nurse ad libitum. Within the first week of life, the lambs and ewes were transferred from the ISU Agricultural Station to the University of Iowa Animal Care and Use Committee.

Lambs were anesthetized with 12 mg/kg of thiopental sodium (Abbott Laboratories, Abbott Park, IL), intubated, and ventilated with a mixture of halothane (1–2%), oxygen (33%), and nitrous oxide (66%). Polyethylene catheters (PE-90, ID = 0.86 mm, OD = 1.27 mm; Intramedic, Franklin Lakes, NJ) were inserted in the lamb’s left femoral artery and vein and sutured in place. The catheter was tunneled subcutaneously and secured to the back of the lamb using porous elastic bandages. Ampicillin (Sigma, St. Louis, MO) was administered at the completion of surgery (2 g im) and every 12 h for 48 h (1 g im). After surgery, the lamb was returned to an individual pen with its mother.

Experimental Protocol

The physiological studies were begun 3 days after surgical preparation. The morning of the experiment, the lamb was transferred to the laboratory, weighed, and placed in a sling-frame assembly, allowing the lamb to return to baseline before administration of the next dose. After a 1-h recovery period, resting MABP and HR were again recorded, and baroreflex curves were determined by producing ramp changes in MABP with continuous intravenous infusion of increasing doses of phenylephrine (5–40 μg·kg⁻¹·min⁻¹) or nitroprusside (5–40 μg·kg⁻¹·min⁻¹) over a 3-min period, using a Harvard infusion pump. A 30-min recovery period was allowed before the alternative drug was administered. Upon completing baroreflex curves, and allowing a 1-h recovery period, the ganglionic blocking agent tetra-ethylammonium bromide (TEA; 10 mg/kg iv; Sigma) was administered. MABP and HR, which were notable for a lack of spontaneous variability, were averaged over 5 min beginning 3 min after the injection. Finally, after a 2-h recovery period to allow hemodynamic parameters to return to baseline values, MABP and HR were again recorded before and 1 h after administration of the ANG II type 1 receptor antagonist losartan (10 mg/kg iv).

Lambs were allowed to recover for 2 days before undergoing a second day of experiments, consisting of baseline MABP and HR measurements, and dose responses to phenylephrine (2, 5, and 10 μg/kg iv) were performed in a similar manner to that for ANG II. Baroreflex curves using phenylephrine and nitroprusside were again performed as previously described. After a 1-h recovery period, lambs then received the nitric oxide synthase inhibitor NOS- nitro-l-arginine (L-NNA; 25 mg/kg iv). MABP and HR were again recorded for 15 min, beginning 15 min after administration of L-NNA.

Femoral and Mesenteric Artery Contractile Responses

After another 2-day recovery period, the lambs were killed with intravenous pentobarbital sodium (50 mg/kg; Abbott Laboratories), and femoral and mesenteric arteries were collected. Branch femoral and mesenteric artery segments with internal diameters of 100–150 μm were cleansed of adherent connective tissue and sectioned into rings on the day of collection. The endothelium was left intact, and the rings were mounted within a small-vessel myography apparatus (model 610; Danish Myotechnology, Aarhus, Denmark) using 40-μm stainless steel wires. Contractile responses were recorded with an eight-channel MacLab SE and stored on a Power Macintosh G3 computer. The length-tension relationship was defined experimentally to 90 mmol/l KCl at varying passive stretch. Passive stretch was set at 80% of the tension required to obtain peak responses to KCl (1.2 mN) for both vessel types, and the rings were allowed to equilibrate in bicarbonate-buffered physiological salt solution (PSS; composition as follows (in mmol/l): 130 NaCl, 4.7 KCl, 1.18 CaCl₂, 1.6 MgSO₄, 7H₂O, 14.9 NaHCO₃, 1.6 CaCl₂·H₂O, 5.5 dextrose, and 0.03 mM Na₂·EDTA (pH 7.30) aerated with a mixture of 95% O₂ and 5% CO₂ at 37°C for 60 min before the start of experimentation.

The contractile response of each vessel to 120 mmol/l KCl was first recorded to allow normalization of subsequent vascular responses. The vessels were then reequilibrated to their baseline with multiple washes of PSS before measurement of vasoconstrictor responsiveness. Cumulative concentration-response curves to KCl (4–100 mmol/l) were performed in a similar manner to that for ANG II. Norepinephrine (NE; 10⁻⁹ to 10⁻⁵ mol/l), and endothelin-1 (ET-1; 10⁻¹¹ to 10⁻⁷ mol/l) were conducted with addition of increasing concentrations of the agent under study before loss of the preceding vascular response. Arteries were reequilibrated to their baseline with multiple washes of PSS between vasoconstrictor agents. To investigate potential alterations in cyclic nucleotide-mediated vasodilation, separate washes of PSS before measurement of vasoconstrictor responsiveness were performed as previously described. After a 1-h recovery period, lambs then received the nitric oxide synthase inhibitor NOS- nitro-l-arginine (L-NNA; 25 mg/kg iv). MABP and HR were again recorded for 15 min, beginning 15 min after administration of L-NNA. All procedures were performed within the regulations of the Animal Welfare Act and the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of Iowa Animal Care and Use Committee.

MABP and HR to return to baseline before administration of the next dose. After a 1-h recovery period, resting MABP and HR were again recorded, and baroreflex curves were determined by producing ramp changes in MABP with continuous intravenous infusion of increasing doses of phenylephrine (5–40 μg·kg⁻¹·min⁻¹) or nitroprusside (5–40 μg·kg⁻¹·min⁻¹) over a 3-min period, using a Harvard infusion pump. A 30-min recovery period was allowed before the alternative drug was administered. Upon completing baroreflex curves, and allowing a 1-h recovery period, the ganglionic blocking agent tetra-ethylammonium bromide (TEA; 10 mg/kg iv; Sigma) was administered. MABP and HR, which were notable for a lack of spontaneous variability, were averaged over 5 min beginning 3 min after the injection. Finally, after a 2-h recovery period to allow hemodynamic parameters to return to baseline values, MABP and HR were again recorded before and 1 h after administration of the ANG II type 1 receptor antagonist losartan (10 mg/kg iv).

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Computation and Data Analysis

The number of animals examined was based on power calculations assuming a normal distribution with equal variances, limiting the alpha error to 0.05 and a sample size sufficient to identify a 33% increase in the response to a given intervention (for which we used the blood pressure response to TEA). To achieve a power of 0.80, a sample size of six animals per group was needed.

The changes in HR in response to alterations in MABP were used to generate the baroreflex curves. Data points sampled every 5 s were analyzed with a logistic sigmoid function (GraphPad Software, San Diego CA) according to the following equation: \( HR = P_4 + P_1/[1 + \exp(P_2 (MABP - P_3))] \), where \( P_1 \) is the range between the upper and lower plateaus, \( P_2 \) is a coefficient used to calculate the gain as a function of pressure, \( P_3 \) is the MABP at the midrange of the curve, and \( P_4 \) is the lower plateau (18). The gain (maximal slope) of the curve was calculated from the first derivative of the above equation. Threshold pressure (lowest pressure that produces a decline in HR) and saturation pressure (pressure necessary to achieve maximal inhibition of HR) were calculated from the third derivative of the equation (18). For an individual animal, the parameters describing the HR-MABP baroreflex relationship where calculated for both days tested and then averaged together before the final analysis. Physiological parameters, including baroreflex curve parameters, and maximal hemodynamic and vascular responses were compared using Student’s unpaired, two-tailed \( t \)-test (with significance at \( P < 0.05 \)). Concentration-responses to the vasoactive agents were compared using ANOVA, factoring for treatment group and dose. If the \( F \)-statistic identified significant differences (\( P < 0.05 \)), pairwise comparisons were made using the Tukey test, with \( P < 0.05 \) considered significant. All statistical analyses were performed using SAS System 9 for Microsoft Windows (SAS Institute, Cary, NC). All values are presented as means ± SE.

RESULTS

Age, weight, arterial pH, blood gases, and hematocrit were similar between the two groups at the start of the experiments (Table 1). Baseline MABP and HR were similar between the groups and did not differ between the first and second experimental day (Table 1).

Table 1. Growth, arterial blood, and hemodynamic parameters for control and early gestation dexamethasone-exposed lambs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dexamethasone Exposed</th>
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<tbody>
<tr>
<td>Age, days</td>
<td>11 ± 1</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>7.05 ± 0.72</td>
<td>7.61 ± 0.74</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Twin gestation*</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.01</td>
<td>7.45 ± 0.01</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>33 ± 1</td>
<td>33 ± 1</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>96 ± 3</td>
<td>98 ± 3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>30 ± 2</td>
<td>31 ± 3</td>
</tr>
<tr>
<td>Heart rate, beats/min†</td>
<td>226 ± 21</td>
<td>249 ± 9</td>
</tr>
<tr>
<td>SBP, mmHg†</td>
<td>98 ± 4</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>DBP, mmHg†</td>
<td>57 ± 3</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>MABP, mmHg†</td>
<td>74 ± 3</td>
<td>77 ± 1</td>
</tr>
<tr>
<td>Heart rate, beats/min‡</td>
<td>208 ± 20</td>
<td>221 ± 10</td>
</tr>
<tr>
<td>MABP, mmHg‡</td>
<td>75 ± 4</td>
<td>77 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE for six animals in each group. Age and weight reflect values from first day of the study. SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure. Values were obtained on first (†) and second (‡) day of the study. *Only one lamb from each twin gestation was used for the study.

The peak change in MABP in response to 20, 50, and 100 ng/kg ANG II was similar in the two groups, although the maximal decrease in HR to 50 and 100 ng/kg ANG II was greater in dexamethasone-exposed compared with control lambs (Fig. 1). Maximal changes in MABP and HR to phentolamine (2, 5, and 10 µg/kg) were similar in control and dexamethasone-exposed lambs (Fig. 2).

Although resting MABP and HR were not different between groups, early gestation exposure to dexamethasone resulted in a significant shift in the baroreflex curve toward the right, or higher pressure (Fig. 3 and Table 2). In particular, the baroreflex curve midpoint (\( P_3, 75 \pm 2 \) vs. \( 84 \pm 3 \) mmHg) and threshold pressure (\( 55 \pm 3 \) vs. \( 68 \pm 4 \) mmHg) were significantly increased in the dexamethasone-exposed group, indicating a shift of the baroreflex curve relating MABP and HR to the right. Upper and lower plateaus of HR, as well as the gain and saturation pressure of the baroreflex curves, were not statistically different.

The changes in MABP and HR in response to intravenous injections of TEA, l-NNA, and losartan are depicted in Fig. 4. After ganglionic blockade with TEA, the magnitude of the decrease in MABP and HR was significantly (\( P < 0.05 \)) greater in dexamethasone-exposed lambs than in control animals. Dexamethasone-exposed lambs also displayed a greater increase in MABP with l-NNA compared with control lambs, although no differences in the HR responses were detected. Finally, blockade of ANG II type 1 (AT\(_1\)) receptors with losartan resulted in similar decreases in MABP but a greater decrease in HR in the dexamethasone-exposed lambs.
Vascular Reactivity

**Responses to voltage-dependent calcium channel activation.** No effect of treatment group was identified on the maximal responses of femoral and mesenteric artery segments to KCl (120 mM): femoral, 6.43 ± 2.29 vs. 6.99 ± 2.36 mN; mesentery, 7.59 ± 1.25 vs. 6.80 ± 0.85 mN for control and dexamethasone-exposed, respectively. The mesenteric and femoral artery cumulative concentration vasoconstrictive responses to KCl were also not significantly altered by dexamethasone exposure (Fig. 5).

**Responses to second messenger-dependent vasoconstrictors.** Dexamethasone exposure tended to attenuate vasoconstrictive responses of systemic microvessels. Specifically, compared with control responses, femoral and mesenteric arteries from dexamethasone-exposed lambs displayed decreased responsiveness to NE and ET-1, respectively (Fig. 5). Femoral artery response to ET-1 and mesenteric artery response to NE were similar in both groups.

**Responses to vasodilators.** There was no significant effect of early gestation dexamethasone exposure on femoral arterial responses to sodium nitroprusside or forskolin (Fig. 6).

**DISCUSSION**

Numerous studies have documented adult-onset blood pressure elevation after fetal nutrient deprivation or exposure to excess glucocorticoids (29). Potential contributions of renal, vascular, and autonomic mechanisms to the programming of postnatal blood pressure have previously been suggested, although consensus is lacking (29). The major findings of this study include the observations that, in newborn lambs exposed to exogenous glucocorticoids early in gestation, the MABP-HR baroreflex relationship is shifted toward higher pressure and that these animals display heightened blood pressure responses to ganglionic and nitric oxide synthase blockade. These altered cardiovascular responses are present before the development of systemic hypertension and therefore are not a consequence of programmed hypertension but may be important contributors to the development of the phenotype.

Although it is well established that the baroreflex provides an important buffering mechanism to counteract short-term fluctuations in blood pressure, more recent evidence also supports a role for baroreceptors in long-term control of blood pressure via regulation of sympathetic activity and sodium excretion (25). Alterations in baroreflex function have previously been demonstrated in animal models of fetal programming, suggesting the arterial baroreflex may impact the development or maintenance of in utero programmed hypertension. In the offspring of rats fed a low-protein diet, the HR-baroreflex response curve is significantly shifted toward high pressure (37). The HR baroreflex is also shifted to the right in 40-month-old sheep exposed to dexamethasone at the end of the first month of gestation (11). However, in both of these studies, the programmed animals were already hypertensive, and resetting of the baroreflex could have been a consequence of hypertension. In contrast, our findings demonstrate that the HR baroreflex is shifted toward higher pressure and that these lambs display heightened blood pressure responses to ganglionic and nitric oxide synthase blockade. These altered cardiovascular responses are present before the development of systemic hypertension and therefore are not a consequence of programmed hypertension but may be important contributors to the development of the phenotype.

### Table 2. Parameter values describing baroreflex control of heart rate in control and dexamethasone-exposed newborn lambs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Dexamethasone Exposed</th>
</tr>
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<tbody>
<tr>
<td>Upper plateau (P尤 + P1尤), beats/min</td>
<td>279 ± 16</td>
<td>289 ± 6</td>
</tr>
<tr>
<td>Lower plateau (P1), beats/min</td>
<td>107 ± 11</td>
<td>113 ± 7</td>
</tr>
<tr>
<td>Gain, beats·min⁻¹·mmHg⁻¹</td>
<td>-5.28 ± 0.42</td>
<td>-6.28 ± 0.76</td>
</tr>
<tr>
<td>Curve midpoint (P2), mmHg</td>
<td>75 ± 2</td>
<td>84 ± 3*</td>
</tr>
<tr>
<td>Threshold, mmHg</td>
<td>55 ± 3</td>
<td>68 ± 4*</td>
</tr>
<tr>
<td>Saturation, mmHg</td>
<td>96 ± 4</td>
<td>105 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE for six animals per group. P尤 range between upper and lower plateaus; P1尤, lower plateau; P尤, MABP at the midrange of the curve. Values were obtained after averaging two separate determinations of baroreflex for each animal. *P < 0.05 compared with control.
Flex is reset before the development of hypertension and suggest abnormalities in autonomic function may contribute, rather than result from, the hypertension. Resetting of the baroreflex before changes in blood pressure has previously been shown in several hypertensive rat models (14, 15). The mechanisms and significance of resetting of the baroreflex remain to be defined. The known role of the renin-angiotensin system in regulating baroreflex function and the concurrent finding that AT1 receptor expression within select brain cardiovascular centers is increased in fetuses and adults exposed to dexamethasone early in gestation (10), whereas AT1 receptor expression is increased in the subfornical organ and the vascular organ of the lamina terminalis in offspring of protein-restricted rats. The accentuated changes in HR in response to ANG II receptor stimulation or blockade in the dexamethasone-exposed lambs relative to controls, in the absence of differences in changes in blood pressure, further support the concept that alterations in the renin-angiotensin system contribute to changes in baroreflex function and programming of hypertension. The finding that both stimulation and inhibition of angiotensin receptors resulted in greater slowing of the HR in dexamethasone-infused compared with control animals may be related to a number of factors, including 1) altered distribution or signaling of AT1 and ANG II type 2 receptors within cardiovascular centers within the brain, 2) accessibility of the agents to cardiovascular centers with and without a blood-brain barrier, and 3) differences in subpopulations of neurons and other neurotransmitter pathways. Ultimately, these differences likely result in distinct effects on sympathetic and parasympathetic drive to the heart.

We cannot rule out the contribution of a renal mechanism contributing to increased sympathetic tone. Previous studies in rats and sheep demonstrate that perinatal environments which ultimately result in hypertension in the offspring are associated with abnormal kidney morphology, including reduced nephron number (49, 50). We did not examine the kidneys of the animals in our study. However, it is possible that underlying renal abnormalities may have contributed to the apparent increase in sympathetic tone in the dexamethasone-exposed lambs (17).

Vascular dysfunction has been hypothesized to explain the relationship between fetal growth retardation and the future development of hypertension. Studies of hypertensive offspring of rats fed a caloric or protein-restricted diet demon-
strate increased contractile responses and impaired small-artery endothelium-dependent and -independent responses (20, 34, 35). In particular, these animals display reduced vascular smooth muscle activity of the NO-cGMP pathway (19, 36). Fetuses of dietary-restricted pregnant ewes display blunted femoral vasodilatory responses to ACh and bradykinin, as well as nitroprusside, suggesting impaired smooth muscle sensitivity to NO (32, 33). Finally, in human infants and children, low birth weight has been shown to be associated with impaired vascular responsiveness to ACh, but not nitroprusside, findings reflective of endothelial dysfunction (26, 27).

In view of these previous studies, we were surprised to find that blockade of nitric oxide production with L-NNA produced a greater increase in blood pressure in the dexamethasone-exposed lambs. In vivo, blockade of NO synthesis may promote increased blood pressure by the following two mechanisms: loss of peripheral vasodilator tone and enhanced central sympathetic drive. With regard to peripheral mechanisms, the greater pressor response observed in dexamethasone-exposed lambs after L-NNA suggests either increased endogenous NO production or enhanced smooth muscle sensitivity to NO in these animals. The attenuated contractile responses to NE and ET-1 seen in femoral and mesenteric artery from dexamethasone-exposed lambs are also consistent with enhanced NO-mediated vasorelaxation. Although the current study did not examine NO-dependent vasodilation in isolated vessels, we previously reported early gestation dexamethasone exposure had no effect on ovine coronary or mesenteric artery vasodilatory responses to nitroprusside or the cGMP analog 8-bromo-cGMP (42). Taken together, these findings suggest that, early in life, peripheral NO production is enhanced after early gestation exposure to glucocorticoids. Differences in species, underlying adverse intrauterine influence, timing of the events, vessels studied, and methodologies may contribute to the
differences in findings between our study and those of other investigators.

It should also be recognized that nitric oxide modulates autonomic function at several sites within the brain and exerts tonic central constraint on sympathetic outflow (38, 46). Given that L-NNA, as used in this study, is known to cross the blood-brain barrier, central inhibition of NO synthase may contribute, in part, to the increases in blood pressure after L-NNA, particularly in dexamethasone-exposed animals.

There are several limitations of the study. Maternal food intake, which could be influenced by dexamethasone treatment and/or zygosity, was not measured. Animals of both genders and from single and twin gestations were also used for the studies. Work by a number of investigators have found sex-specific differences in the programming of hypertension and glucose intolerance (29). Twin gestation may also predispose to physiological programming (44). These effects may be related to differences in nutritional status and/or the development of the hypothalamic-pituitary-adrenal axis [for review see McMillen and Robinson (29)]. Finally, lambs were gently restrained in a sling-frame assembly for the study. Differences in the stress response to this intervention may also have contributed to our findings.

Perspectives

We have demonstrated that in this sheep model, “programming” resets the baroreflex and likely modifies sympathetic efferent tone. Furthermore, programming by exposure to early gestation glucocorticoids appears to augment NO-mediated vasodilatation early in life. The interaction of these two systems in long-term blood pressure regulation requires further investigation. Alterations in either the “buffering” capability of NO-mediated vasodilation or autonomic control of circulatory function may ultimately contribute to the development of “programmed” hypertension. Further understanding of how the perinatal environment effects physiological systems is necessary to enable the development of interventions aimed at alleviating the deleterious consequences of intrauterine programming.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance of Mark A. Hart in the preparation of this manuscript.

GRANTS

This study was supported by National Institutes of Health Grants ES-012268 (to J. L. Segar), HL-04495 (to T. D. Scholz), HL-62483 (to F. S. Lamb), and HD-041922 (to Physician Training Program in Neonatal Biology and R. D. Roghair). F. S. Lamb is supported by an Established Investigator Award from the American Heart Association.

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