Hepatic glucose regulation and metabolism in adult sheep: effects of prenatal betamethasone

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Submitted 31 January 2005; accepted in final form 27 May 2005

Sloboda, Deborah M., Timothy J. M. Moss, Shaofu Li, Dorota A. Doherty, Ilias Nitos, John R. G. Challis, and John P. Newnham. Hepatic glucose regulation and metabolism in adult sheep: effects of prenatal betamethasone. Am J Physiol Endocrinol Metab 289: E721–E728, 2005.—Fetal exposure to synthetic glucocorticoids in sheep results in increased fetal hepatic 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and corticosteroid-binding globulin (CBG) protein levels and insulin resistance in postnatal life. The aim was to determine whether these changes persisted to adulthood and whether alterations in mediators of hepatic glucocorticoid and glucose regulation contributed to changes in metabolism. Pregnant ewes or their fetuses received either repeated intramuscular saline (MS, F5) or betamethasone injections (0.5 mg/kg; M4, F4) at 104, 111, 118, and 124 days of gestation (dG), or a single betamethasone injection at 104 dG followed by saline at 111, 118, and 124 dG (M1, F1). Offspring were catheterized at 2 and 3 yr of age and given an intravenous glucose challenge (0.5 mg/kg). Hepatic tissue was collected at 3.5 yr. At 2 yr of age, basal plasma insulin was elevated in M4 offspring and at 3 yr of age was elevated in F4 offspring. Basal insulin-to-glucose ratio was significantly elevated in M4 offspring at 2 yr of age and elevated in M1, M4, and F4 offspring at 3 yr of age. All betamethasone treatments resulted in significant increases in hepatic glucose-6-phosphatase (G-6-Pase) activity. Hepatic glucocorticoid receptor protein levels were not altered in M1 and M4 offspring but were increased in F1 and F4 offspring. Hepatic CBG protein levels were lower in F4 but not F1 offspring and were unchanged from control in M1 and M4 offspring. Prenatal betamethasone exposure results in elevated hepatic G-6-Pase activity in adulthood and may contribute to long-term changes in metabolism.

INTRAUTERINE FACTORS ARE IMPORTANT DETERMINANTS OF THE RISK OF DEVELOPING A VARIETY OF ADULT DISEASES (3, 11, 18). IN HUMANS, LOW BIRTH WEIGHT HAS BEEN ASSOCIATED WITH IMPAIRED GLUCOSE TOLERANCE AND INSULIN RESISTANCE IN ADULTHOOD (7, 20, 21) AND IS RELATED TO LEVELS OF FASTING PLASMA CORTISOL LEVELS, ELEVATED SYSTOLIC BLOOD PRESSURE, Plasma glucose and triglyceride levels, and insulin resistance in adult men (19).

Although mechanisms linking intrauterine growth restriction and metabolic function are poorly understood, studies suggest that prenatal glucocorticoids exposure can restrict fetal growth and permanently alter metabolic enzymes in the liver. Glucose intolerance in adult rats exposed to maternal dexamethasone in utero has been associated with elevated expression of hepatic glucocorticoid receptor (GR) and glucocorticoid-sensitive enzymes involved in glucose regulation such as phosphoenolpyruvate carboxykinase and glucokinase (10, 16, 17). Local hepatic availability of glucocorticoids is regulated in part by corticosteroid-binding protein (CBG), GR, and the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). We have shown previously that repeated maternal glucocorticoid administration resulted in decreased fetal growth and significantly elevated fetal hepatic CBG and 11β-HSD1 levels (25, 26). These data suggest that prenatal exposure to glucocorticoids alters intra-hepatic glucocorticoids levels, potentially contributing to changes in the expression of metabolic enzymes. Furthermore, we have demonstrated that maternal betamethasone administration results in significant increases in offspring insulin responses to a glucose load at 6 mo and 1 yr of age in a pattern that resembles insulin resistance in type 2 diabetes (14).

The long-term effects of fetal exposure to glucocorticoids during pregnancy are of direct clinical relevance. Since the first trial in 1972 (9), the administration of synthetic glucocorticoids to women threatened with preterm delivery has become standard obstetric practice. Although repeated courses of glucocorticoids in general are no longer recommended (1), recent surveys suggest that clinicians may still be administering multiple courses (12). The long-term effects of antenatal glucocorticoid treatment in humans are unknown. Individuals from the first reported trial of single-course treatment (9) are currently being studied, and ongoing randomized controlled trials of repeated treatments have not been completed.

Long-term effects of fetal exposure to glucocorticoids in sheep depend on the route of administration. In early studies, we (8, 15) demonstrated that fetal intramuscular injections of synthetic glucocorticoid (betamethasone) significantly improved fetal lung function and did not result in growth restriction. Furthermore, we (14, 24) have demonstrated that maternal intramuscular injection of betamethasone significantly altered postnatal hypothalamic-pituitary-adrenal (HPA) axis activity in offspring but direct fetal glucocorticoid injection did not. We (13) have since shown that fetal circulating levels of betamethasone after maternal injection differ from those observed after fetal injection. Cumulative exposure of the fetus to betamethasone was higher after fetal injection than after ma-
ternal injection, but the length of exposure was shorter after fetal injection. This provides us with two models of glucocorticoid exposure with markedly different exposure times. It appears that the differential effects observed in these two routes of injection are due to differences in the duration of fetal exposure to betamethasone. The effects of fetal glucocorticoid injection on intrahepatic regulation of glucocorticoids and glucose are unknown.

The aims of the present study were to determine whether, after maternal intramuscular betamethasone injection, alterations in fetal intrahepatic glucocorticoid regulation persisted to adulthood; whether these changes were associated with long-term hepatic glucose regulation and changes in whole body glucose metabolism; and whether fetal intramuscular injections had similar effects. We hypothesized that maternal betamethasone injection would result in increased intrahepatic glucocorticoid levels that contribute to increases in hepatic glucose production and alterations in whole body glucose metabolism. We anticipated that fetal betamethasone injections would not have these effects.

MATERIALS AND METHODS

All experimental procedures were approved by the Animal Experimentation Ethics Committee of The University of Western Australia.

Experimental Procedures

**Prenatal treatments.** Pregnant ewes bearing singleton fetuses were allocated randomly to receive either maternal or fetal injections of saline and/or betamethasone (Table 1). All animals were injected intramuscularly with 150 mg of medroxyprogesterone acetate (Depo Provera; Upjohn, Rydalmere, Australia) at ~100 days of gestation to reduce pregnancy losses due to subsequent glucocorticoid treatment (14, 24). Saline-treated animals were injected with normal saline at 104, 111, 118, and 124 days of gestation (maternal saline, MS; fetal saline, FS); single betamethasone-treated animals were injected with betamethasone at 104 days of gestation and saline at 111, 118, and 124 days of gestation (M1, F1); repeated betamethasone-treated animals were injected with betamethasone at 104, 111, 118, and 124 days of gestation (M4, F4). Maternal betamethasone (Celestone Chronodose; Schering Plough, Baulkham Hills, Australia) injections were given intramuscularly in a dose of 0.5 mg/kg body wt; fetal saline injections were of a comparable volume (5–6 ml). Fetal injections were allowed free access to water. Basal arterial blood samples (5 ml) were drawn at 30 min, 15 min, and immediately before the administration of an intravenous bolus of glucose (0.5 g/kg Baxter) followed by a 10-ml saline flush. Arterial samples (5 ml) were collected at 5, 10, 20, 30, 60, 90, 120, and 180 min after glucose administration and centrifuged at 1,000 g for 10 min at 4°C, and plasma was collected and stored at −80°C for further analysis. All challenges were administered between 0800 and 0900 to minimize the impact of circadian variability on measurements. Catheters were removed after the completion of experiments.

**Intravenous glucose challenge at 2 and 3 yr of postnatal age.** At both 2 and 3 yr of postnatal age, offspring underwent aseptic surgery to implant femoral arterial and venous catheters (halothane anesthesia, 1–2% in O2, following induction with ketamine-xylazine) and were allowed free access to water. Basal arterial blood samples (5 ml) were drawn at 30 min, 15 min, and immediately before the administration of an intravenous bolus of glucose (0.5 g/kg Baxter) followed by a 10-ml saline flush. Arterial samples (5 ml) were collected at 5, 10, 20, 30, 60, 90, 120, and 180 min after glucose administration and centrifuged for 10 min at 4°C, and plasma was collected and stored at −80°C for further analysis. All challenges were administered between 0800 and 0900 to minimize the impact of circadian variability on measurements. Catheters were removed after the completion of experiments.

**Measurement of glucose and insulin concentrations.** Glucose was measured in aliquots (100 μl) of whole blood by the glucose oxidase method (Bayer, RapidLab 1260, Perth, WA, Australia). Immune-reactive plasma insulin concentrations were measured using a commercially available ovine insulin enzyme-linked immunosorbent assay (ELISA; Mercodia, Uppsala, Sweden). The intra-assay coefficient of variation was 6%; the interassay coefficient of variation was 9%.

Western blot analysis. CBG, GR, and 11β-HSD1 proteins were identified by Western blotting as described previously (26). Briefly, total protein was extracted from frozen liver samples in RIPA lysis buffer. A total of 14 samples from maternal treatment groups (MS = 5, M1 = 4, M4 = 5) and 15 samples from fetal treatment groups (FS = 4, F1 = 7, F4 = 4) were available for analysis. Protein concentrations were determined using the Bradford assay (5). Proteins were separated by electrophoresis on polyacrylamide gels, transferred onto PVDF membranes (Bio-Rad Laboratories), and incubated overnight at 4°C in blocking solution (5% skim milk powder wt/vol in PBS + Tween-20). Blots were incubated with primary polyclonal antibodies; ovine CBG (for maternal treatments 1:5,000, for fetal treatments 1:3,000) generated in our laboratories (4); ovine 11β-HSD1 (for maternal treatments 1:2,000, for fetal treatments 1:10,000) generously donated by Dr. Kaiping Yang (30); and human GR (for maternal treatments 1:100, for fetal treatments 1:100; Santa Cruz Biotechnology). Blots were incubated with secondary antibodies conjugated to horseradish peroxidase (anti-rabbit Ig-horseradish peroxidase; Amersham Life Sciences), and detection of specific protein bands was accomplished using a chemiluminescence detection system (SuperSignal West Pico Chemiluminescent Substrate, Pierce). All blots were reincubated with anti-β-actin (Sigma) as an internal control to allow for corrections in gel loading and transfer. Band density for both the protein of interest and β-actin was quantified by densitometry.
Table 2. Basal glucose and insulin levels at 2 and 3 yr of postnatal age in offspring treated with either prenatal maternal or fetal betamethasone

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>2 yr of Age</th>
<th>3 yr of Age</th>
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<tbody>
<tr>
<td></td>
<td>Glucose, mmol/l</td>
<td>Insulin, ng/ml</td>
</tr>
<tr>
<td>MS</td>
<td>3.32±0.22</td>
<td>0.34±0.17</td>
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<tr>
<td>M1</td>
<td>3.24±0.62</td>
<td>0.38±0.18</td>
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<tr>
<td>M4</td>
<td>3.60±0.47</td>
<td>0.80±0.50*</td>
</tr>
<tr>
<td>FS</td>
<td>3.45±0.58</td>
<td>0.61±0.24</td>
</tr>
<tr>
<td>F1</td>
<td>3.37±0.61</td>
<td>0.33±0.20*</td>
</tr>
<tr>
<td>F4</td>
<td>3.23±0.52</td>
<td>0.51±0.16</td>
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</tbody>
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Values are presented as means ± SE. *P < 0.05 M4 vs. MS, FS vs. F1, F4 vs. F1.

using Scion Image Analysis software (Scion). The results are expressed as the ratio of protein to β-actin as relative optical density (ROD) units.

Glucose-6-phosphatase assay. Hepatic glucose-6-phosphatase (G-6-Pase) activity was determined by measuring phosphate production from glucose 6-phosphate, as described previously (2, 6). Briefly, liver (~150–200 mg) was homogenized in 2 ml of ice-cold 0.25 M sucrose and assayed within 30 min. Two homogenates per tissue were assayed, and each homogenate was assayed in duplicate. Diluted homogenate (100 μl) was incubated at 37°C in an assay mixture containing 62.5 mM sucrose, 0.25 mM EDTA, 25 mM cacodylate buffer (pH 6.5), and 24 mM glucose 6-phosphate. The reaction was stopped (after 0 and 10 min) by the addition of a 2-ml mixture of molybdate and 2% arsenite-citrate was added, left to incubate at room temperature for 15 min, and assayed for inorganic phosphate.

Statistical Analysis

Results are expressed as means ± SE. For glucose challenge data, a comparison of group means was made using analysis of variance (ANOVA; SAS, Cary, NC, and S-PLUS, Mathsoft, Seattle, WA). In all cases, basal values represent the mean value of the three samples drawn before the administration of the intravenous bolus glucose injection (time 0). The experimental design did not allow us to examine possible sex-specific effects on outcome variables. The numbers of male and female offspring were distributed evenly among different treatment groups. To assess the overall effect of prenatal betamethasone on the response patterns to the challenge, we calculated the areas under the response curves (AUC) for each group between 5 and 180 min after glucose. This calculation permitted us to resolve occasional missing values where sample collection may have been impaired. Hepatic CBG, 11β-HSD1, and GR protein levels were expressed as ROD protein-to-β-actin ratio, and all results were analyzed using a one-way ANOVA (SigmaStat; Jandel Scientific, San Rafael, CA). In all cases, statistical significance was accepted for values P < 0.05.

RESULTS

Postnatal Insulin Levels and Glucose Tolerance

Prenatal betamethasone treatment significantly elevated basal insulin levels in M4 offspring at 2 yr of age (P = 0.006), and at 3 yr of age insulin levels tended to be higher than in MS offspring, but this difference was no longer statistically significant. Basal insulin levels were significantly lower in F1 offspring at 2 yr of age (P = 0.003) and were significantly higher than control in F4 offspring at 3 yr of age (P = 0.008;
Table 2). At 2 yr of age, basal insulin-to-glucose ratio (I:G) was significantly elevated in M4 offspring (Fig. 1, A and C, \( P = 0.02 \)) and in M1 and M4 offspring at 3 yr compared with controls (\( P = 0.025 \) and \( P = 0.031 \), respectively). I:G in F1 and F4 offspring was not different from control (FS) offspring at 2 and 3 yr of age (Fig. 1D).

Blood glucose and plasma insulin responses to an intravenous glucose bolus at 2 yr of postnatal age were not signifi-
significantly affected by prenatal betamethasone treatment (Fig. 2, A–D), but insulin responses tended to be higher in M1 and M4 offspring compared with control offspring. Blood glucose and plasma insulin responses in offspring at 3 yr of postnatal age were not affected by prenatal treatment with betamethasone (Fig. 3, A–D). Insulin responses in the F4 group were not significantly affected by prenatal betamethasone treatment, but insulin responses in F4 offspring tended to be higher than those of FS offspring. Consequently, areas under the glucose and insulin response curves (AUC) were not significantly affected by prenatal glucocorticoid treatment compared with controls (data not shown).

**Hepatic G-6-Pase Activity**

Prenatal betamethasone treatment resulted in a significant increase in hepatic G-6-Pase activity in adult offspring. This increase was observed in all betamethasone-treated offspring (M1, M4, F1, F4, *P* < 0.001; Fig. 4) compared with relevant control offspring (MS, FS).

**Hepatic CBG, GR, and 11β-HSD1 Protein Levels**

Hepatic CBG protein (57 kDa) levels were not significantly different at 3.5 yr of age in M1 or M4 offspring, but highest levels were observed in M4 offspring (*P* = 0.003 and *P* = 0.017 respectively; Fig. 5). Hepatic GR protein levels in M1, M4, and F4 offspring were not different from relevant controls (Fig. 6), but F1 offspring demonstrated a significant elevation in hepatic GR protein levels (*P* = 0.041; Fig. 6). Prenatal betamethasone treatment had no effect on hepatic 11β-HSD1 protein levels (data not shown).

**DISCUSSION**

Our study demonstrated a significant increase in the activity of hepatic G-6-Pase in adult sheep that were exposed in utero to either single or repeated doses of betamethasone administered either to the mother or to the fetus. Repeated maternal doses of betamethasone resulted in significantly increased basal insulin levels in offspring at 2 yr of age, and although at 3 yr of age they were not statistically significant they remained high. As a consequence, an elevated basal I:G ratio persists to 3 yr of age compared with control values. These data are consistent with our previous observations: stimulated I:G ratios in these animals at 6 and 12 mo of age were higher in offspring treated with maternal betamethasone (14). Thus it appears that M4 offspring require increased insulin levels to maintain euglycemia up to 3 yr of postnatal age. We (14) have shown previously that prenatal betamethasone administration results in significant elevations in postnatal insulin responsiveness to glucose at 6 mo and 1 yr of age. In the current study, insulin responsiveness was not significantly different between treatment and control groups, reflecting little change in insulin sensitivity. These data therefore suggested that insulin responsiveness in these offspring was ameliorated with increasing postnatal age. Our current data, combined with our previous observations, suggest that alterations in insulin regulation induced by prenatal glucocorticoid exposure evolve over time in
sheep (time course illustrated in Fig. 7). The effects of direct fetal betamethasone injection oppose those observed after maternal injection. The mechanisms regulating the decrease in basal insulin levels in the F1 offspring are unknown but are consistent with our previous observations that F1 and F4 offspring had modestly suppressed basal insulin levels at 1 yr of age (14). Our data have important implications for the design of future investigations of long-term metabolic consequences of in utero adaptations. A single cross-sectional study of postnatal in vivo metabolic responses after birth may provide misleading results. Nevertheless, prenatal maternal betamethasone administration appears to have consistent long-term effects on basal insulin regulation in adult offspring.

G-6-Pase is the rate-limiting enzyme in the glucogenic pathway and regulates the production of glucose by glycogenolysis and gluconeogenesis (28). Glucocorticoids increase G-6-Pase activity and are responsible for regulating hepatic glucose production (29; for review see Ref. 27). In the present study, we found significant elevations in G-6-Pase activity in offspring exposed to prenatal maternal or fetal betamethasone. This increase in G-6-Pase activity was greatest in animals exposed to repeated doses. Although these sheep did not demonstrate increased basal glucose levels, we did observe elevations in the basal I:G ratio in M1 and M4 offspring this age, suggesting that they were able to maintain euglycemia with moderately increased insulin output. Conversely, F1 and F4 offspring demonstrated elevated G-6-Pase activity but normal glucose levels and I:G ratios. The mechanisms regulating these observations are unclear; however, it is possible that the disparity between our physiological and molecular results is due to differences in the timing of the measurements. One strength of our study is that we evaluated metabolic physiology in these animals over a 3-yr time frame (see also Ref. 14), but tissue measurements could be performed at only one time point (3.5 yr). Taken together, these data reinforce the concept that whole body physiology evolves over time (Fig. 7) and that molecular measurements provide a snapshot of events occurring at the moment that tissue was collected.

We have previously demonstrated that maternal betamethasone administration resulted in significant increases in fetal hepatic CBG and 11β-HSD1 levels (26) and that these were associated with a significant elevation in fetal plasma corticosteroid binding capacity and fetal basal glucose levels (25). The present study demonstrates that these alterations do not persist to adulthood; therefore, the observed increase in G-6-Pase activity in M1 and M4 offspring is regulated through mechanisms other than intrahepatic glucocorticoid regulation. Offspring treated with prenatal glucocorticoids in this study demonstrate elevated basal plasma insulin levels (although not statistically significant in M1 and M4 offspring at 3 yr; Table 2). Under normal circumstances, elevated circulating insulin levels reduce hepatic glucose output rapidly by inhibiting

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**Fig. 6.** Hepatic glucocorticoid receptor (GR) protein (97 kDa) levels at 3.5 yr of postnatal age in offspring treated with MS or FS (open circle), M1, F1 (gray triangle), or M4, F4 (filled square). Autoradiogram for GR and β-actin are shown at top. Values are presented as ROD. GR/β-actin ratios are means ± SE. *P < 0.05, FS vs. F1 and F4. Absence of error bars is an indication of small variation.

**Fig. 7.** Summary of postnatal areas under glucose and insulin response curves (AUC) at 6 mo and 1 yr have been published previously (14). Values are presented as means ± SE.
glycogenolysis, through decreasing glycogen phosphorylase activity, and by gradually decreasing G-6-Pase. Elevated G-6-Pase activity in offspring treated with maternal betamethasone may be an indicator of hepatic insulin resistance.

In contrast to the long-term effects of maternal betamethasone treatment, fetal betamethasone administration resulted in significant elevations in GR protein levels that were associated with reduced CBG protein levels. Such alterations in hepatic GR and CBG would be expected to increase intrahepatic glucocorticoid action; therefore, elevated hepatic G-6-Pase activity in these offspring appears to be regulated by an increase in glucocorticoid action (an increase in GR expression and a decrease in CBG expression). Previous studies have demonstrated that glucocorticoid administration to pregnant rats late in gestation resulted in significant increases in GR expression levels and increased postprandial I:G ratios in adult male offspring (16). In offspring treated with fetal betamethasone in our study, this increase in intrahepatic glucocorticoid levels may contribute to hepatic insulin resistance.

Previous studies have shown that glucocorticoid programming of abnormal postnatal metabolism is associated with altered HPA activity (10, 17). We (14, 24, 25) have demonstrated in sheep that maternal betamethasone treatment resulted in elevated HPA axis activity in fetal and postnatal life and elevated insulin responses to a glucose challenge at 1 yr of postnatal age. However, at 3 yr of postnatal age, offspring exposed to maternal betamethasone exhibited significant reductions in basal cortisol levels and moderate reductions in cortisol responsiveness (23). Thus long-term HPA axis function, at least in maternally-treated offspring, is suppressed, suggesting that increased G-6-Pase activity in these animals is not likely due to HPA hyperactivity. It is possible that other factors might be contributing to altered hepatic enzyme activity such as alterations in circulating thyroid hormones (triiodothyronine, thyroxine). Thyroid hormones influence hepatic gluconeogenic enzymes in rats and sheep, and glucocorticoids are known to modulate hypothalamic-pituitary-thyroid activity. It is possible that attenuated cortisol output in M4 animals may have contributed to elevated thyroid activation and subsequent stimulation of hepatic G-6-Pase activity.

In the current study, we demonstrated that maternal or fetal betamethasone administration have differential effects on hepatic GR and CBG protein levels. We have previously shown that maternal but not fetal betamethasone administration resulted in a dose dependent decrease in fetal growth (15) and also that HPA axis function was altered in 1-yr-old offspring of prenatal maternal treatment but not fetal treatment (24). Taken together, these observations suggest that the effects of maternal compared with fetal betamethasone treatment are mediated through different mechanisms. Recently, we have shown (13) that peak fetal plasma betamethasone levels were 10-fold higher after fetal injections than after maternal injections but were not sustained. Fetal plasma levels of betamethasone were detectable for up to 8 h after maternal injection but were undetectable 2 h after direct fetal injection. The effects seen after maternal betamethasone treatment are likely to be the cause of a cumulative duration of betamethasone exposure rather than the total betamethasone dose (13). It is possible that the maternal circulation serves as a reservoir for betamethasone, prolonging the half-life of betamethasone within the fetal circulation. Alternatively, the clearance rate of betamethasone may be higher in the fetus after fetal injections. The mechanisms regulating these possibilities are unknown. Effects of maternal betamethasone administration on the development and function of the placenta are unclear. We (22) have recently reported that repeated doses of maternal betamethasone resulted in a significant reduction in total placental weight late in gestation with differential effects on placental subtypes. These findings support the possibility that the placenta regulates the effects of maternal betamethasone injection. Further investigations into the effects of betamethasone administration on placental endocrinology and growth are currently being completed.

Overall, our data demonstrate alterations in glucose regulation after prenatal glucocorticoid exposure that persist to 3 yr of postnatal age and, importantly, that these responses change with increasing postnatal age. Although the data presented in this study may not be indicative of overt insulin resistance, we have demonstrated significant increases in both insulin-to-glucose ratios and glucose-6-phosphatase activity in offspring exposed to maternal betamethasone injections. Furthermore, we have demonstrated differential effects, depending on the route of administration (fetal vs. maternal prenatal injections). This has never before been shown. Fetal adaptations to prenatal betamethasone exposure may have long-term effects on postnatal hepatic glucose production and result in hepatic insulin resistance.

ACKNOWLEDGMENTS

We thank Dr. Kaiping Yang for the generous donation of the 11β-HSD1 antibody, Drs. K. Poore and A. Fowden for the G-6-Pase assay protocol, and Adrian Jonker for assistance with in vivo challenges and tissue collection.

GRANTS

This study was supported by The National Health and Medical Research Council of Australia (project grant nos. 110301 and 980578) and the Canadian Institutes of Health Research Group in Fetal and Neonatal Health and Development.

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