**Differential timing for programming of glucose homoeostasis, sensitivity to insulin and blood pressure by in utero exposure to dexamethasone in sheep**

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**A B S T R A C T**

Numerous epidemiological studies have related an increased risk of adult-onset cardiovascular and metabolic disease to an adverse intra-uterine environment at critical periods. We have shown that fetal sheep exposed to dexamethasone for only 2 days at 27 days of gestation (term \( \approx 150 \) days) became hypertensive adults, whereas those exposed at 64 days of gestation remained normotensive, as did controls. In the same sheep, now nearly 5 years old, we performed glucose tolerance tests and hyperinsulinaemic euglycaemic clamps to study the insulin sensitivity of glucose, amino acid and non-esterified fatty acid metabolism. Glucose tolerance, calculated as the area under the curve, after intravenous administration of bolus glucose and insulin secretion in response to a glucose challenge were not altered in any group. There were no significant differences in the insulin sensitivity of net whole-body glucose or amino acid uptake. However, suppression of lipolysis by insulin, measured as the proportional decrease in the circulating concentration of non-esterified fatty acids during the hyperinsulinaemic clamp, was \( 69 \pm 1.2 \% \) at steady-state plasma insulin levels (\( \approx 1000 \) m-units/l) in the group exposed to dexamethasone at 27 days of gestation, but only \( 50.8 \pm 6.5 \% \) in the controls (\( P < 0.05 \)). In the group exposed to dexamethasone at 64 days of gestation, the decrease was \( 66.4 \pm 5.1 \% \), which did not reach significance compared with the controls (\( P = 0.10 \)). Thus brief dexamethasone exposure during early gestation programmed hypertension independently of insulin resistance of glucose or amino acid metabolism; however, it did lead to increased insulin sensitivity of the inhibition of lipolysis, which may increase susceptibility to the development of obesity postnatally.

**INTRODUCTION**

Numerous epidemiological studies have shown that small size at birth (for gestational age) is associated with increased incidence of adult-onset diseases or dysfunction, including Syndrome X [hypertension, type II (non-insulin-dependent) diabetes mellitus and hyperlipidaemia] (reviewed in [1,2]). It has been proposed that an adverse intra-uterine environment during a critical stage of development may permanently alter, or ‘programme’, the development of fetal tissues, which enables the fetus to survive, but with adverse consequences in postnatal life. Animal studies to test this hypothesis have imposed perturbations such as moderate to severe maternal undernutrition, or feeding of a low-protein diet throughout pregnancy, and confirmed that restriction of fetal growth leads to elevated blood pressure in the progeny of rats [3–5] and sheep [6]. In contrast, the same perturb-
Changes in the rat have inconsistent effects on postnatal glucose metabolism, such that improved [7], unaltered [8] or impaired [9,10] glucose tolerance or insulin sensitivity in progeny have been variously reported.

Several authors have proposed that the mechanism of developmental programming by an adverse fetal environment is via exposure to excess glucocorticoid hormones [11,12]. Prenatal glucocorticoid exposure retards fetal growth and impairs postnatal function. In rats, administration throughout pregnancy of the 11β-hydroxysteroid dehydrogenase inhibitor carbenoxolone, which blocks the placental inactivation of endogenous glucocorticoids, reduces birth weight and results in hypertension and impaired glucose tolerance in adult progeny [13–15]. Removing the source of glucocorticoids, by maternal adrenalectomy, prevents the development of hypertension in the progeny of carbenoxolone-treated dams [15]. Other studies have exposed the developing fetus to elevated glucocorticoid levels via maternal treatment with the synthetic glucocorticoid dexamethasone, which is poorly metabolized by 11β-hydroxysteroid dehydrogenase. Dexamethasone treatment throughout pregnancy reduces birth weight and results in hypertensive adult progeny in the rat [16]. There is evidence that programming of hypertension in progeny by maternal protein undernutrition in pregnant rats occurs via fetal glucocorticoid exposure, since concomitant treatment with metyrapone throughout pregnancy, to inhibit maternal corticosterone synthesis, also prevents the increase in blood pressure in adult progeny [12]. Conversely, maternal corticosterone replacement during metyrapone treatment of protein-restricted dams produced hypertension in female, but not in male, progeny at 6 weeks of age [12].

While fetal exposure to steroids at most stages of development appears to lead to adult hypertension, the precise mechanisms responsible may vary with the timing of exposure. Treatment of pregnant rats with dexamethasone during the last third of pregnancy reduces birth weight and produces hypertension in adult progeny [17]. Recently we have shown that very brief exposure of the sheep fetus to high levels of dexamethasone, for only 2 days of the 150-day gestation period at a mean of 27 days of gestation, results in hypertensive offspring at 3–4 months of age [18]. This hypertension is amplified with age and is associated with increased cardiac output [19]. Sheep exposed to dexamethasone for 48 h at a mean of 64 days of gestation are normotensive, but nevertheless show reduced sensitivity of the baroreceptor heart rate reflex [19].

Recent studies have suggested that the timing of the programming of postnatal function by an adverse fetal environment might differ between regulatory systems. For example, maternal food intake restriction during the Dutch famine did not affect the basal blood pressure, but did impair the glucose tolerance, of adult offspring [20,21]. Famine exposure during late gestation led to a greater impairment of glucose tolerance than did famine exposure during mid or early gestation, and overall glucose tolerance fell with increasing weight, length or head circumference at birth [20]. Similarly, maternal dexamethasone treatment during the last week, but not the first 2 weeks, of pregnancy in the rat impaired glucose tolerance in adult offspring [22].

Animal studies of maternal nutrition [3,8–10] and glucocorticoid exposure [13,17,22], together with the results of the Dutch famine studies [20,21], suggest that postnatal glucose metabolism may be most susceptible to insults occurring during the last third of gestation, whereas postnatal blood pressure may also be affected by events in the second, and possibly the first, third of gestation. Therefore we propose that the timing of the programming of postnatal blood pressure, glucose homoeostasis and sensitivity to insulin by fetal dexamethasone exposure will also differ. Specifically, we hypothesize that adult hypertension following dexamethasone exposure in early gestation (day 27), and altered baroreflex following dexamethasone exposure in mid gestation (day 64), will not be associated with impaired glucose tolerance or altered insulin sensitivity in the adult sheep.

**MATERIALS AND METHODS**

**Animals**
Sheep were exposed to dexamethasone *in utero* as described previously [18]. Briefly, pregnant ewes were treated with dexamethasone (Decadron; Merck, Sharp and Dohme), given as an intravenous infusion (0.28 mg kg⁻¹·day⁻¹), for 48 h commencing at mean ages of 27 (27D) or 64 (64D) days of gestation. Only female lambs were studied postnatally, due to limited numbers of male progeny. Control female lambs were born to ewes which were exposed to a minimum stress during gestation. Birth weights did not differ between the groups, being 4.7±0.4 kg in the control, 4.9±0.3 kg in the 27D and 4.1±0.4 kg in the 64D group. Lambs were oophorectomized to eliminate effects of oestrous cycles on postnatal function, and carotid loops were inserted at 50 days of age.

Weaning lambs (50 days of age) were fed on grass-dominant pasture supplemented with oats to obtain an energy intake of 6 MJ/kg of dry matter with a higher level of crude protein (16% /kg), to achieve a growth rate of approx. 1 kg/week by the end of the first year. During experimentation, sheep were kept in metabolism cages and provided with food (lucerne chaff/oat chaff mixture, 1:1, w/w) and water *ad libitum*. This diet regimen supplies metabolizable energy of approx. 9 MJ/kg of dry matter and contains 10% crude protein/kg. As each of the experiments was concluded [18,19], sheep were
Glucose tolerance was measured as the area under the glucose concentration curve. Insulin secretion was calculated as the area under the insulin concentration curve, corrected for the area under the glucose concentration curve. Area under the curve was calculated as the area between the baseline concentration and the concentration profile during the intravenous glucose tolerance test, using the Sigma Scan Pro v4 software package (Jandel Scientific Software).

### Measurement of the insulin sensitivity of glucose, amino acid and non-esterified fatty acid metabolism in vivo

The insulin sensitivity of glucose metabolism was measured by hyperinsulinaemic euglycaemic clamp. The basal blood glucose concentration was calculated as the mean of blood glucose concentrations in samples taken 10, 5 and 0 min before beginning the clamp. Human insulin was infused into the venous catheter at 6 m-units insulin \( \text{min}^{-1} \cdot \text{kg}^{-1} \) live weight. Blood samples (0.2 ml) were taken at 5 min intervals throughout the experiment, and blood glucose was analysed immediately after sample collection using a glucometer (HemoCue AB, Angelholm, Sweden). An infusion of glucose (25 %, w/v) was begun 15 min after the insulin infusion, at a rate calculated to restore and maintain euglycaemia. Larger blood samples (2 ml), for measurement of plasma insulin, amino nitrogen and non-esterified fatty acid concentrations, were collected on to ice at \(-10, -5, 0, 60, 75, 90, 105, 120, 140, 160, 180\) and \(210\) min after the start of the insulin infusion. Basal concentrations were calculated as the means of values obtained in the three pre-infusion samples, and steady-state concentrations were calculated as the means of values obtained in the five samples taken during the last hour of the clamp. At the end of the experiment, these samples were centrifuged at \(1800 \, \text{g} \) for \(10\) min at \(4\) °C, and plasma harvested. Plasma samples were stored at \(-20\) °C for subsequent analyses.

The insulin sensitivity of net whole-body glucose uptake was calculated as the steady-state glucose infusion rate (SS-GIR) needed to maintain euglycaemia (averaged across the second hour of the clamp), corrected for the steady-state plasma insulin concentration:

\[
\text{Insulin sensitivity (glucose uptake)} = \frac{\text{SS-GIR (mg of glucose} \cdot \text{min}^{-1} \cdot \text{kg}^{-1})}{\text{steady-state plasma insulin (m-units/l)}}.
\]

The insulin sensitivity of amino acid (AA) or non-esterified fatty acid (NEFA) metabolism was calculated as follows:

\[
\text{Insulin sensitivity (% change in AA or NEFA per 1 m-unit/ml insulin)} = \frac{[(\text{basal AA or NEFA} - \text{steady-state AA or NEFA})/\text{(basal AA or NEFA)}] \times 100}{\text{(steady-state plasma insulin)}}.
\]
where plasma amino acid and non-esterified fatty acid concentrations are in units of mmol/l, and insulin concentration is in units of m-units/l.

The post-hepatic insulin clearance rate was calculated as the ratio of the exogenous insulin infusion rate to the steady-state plasma insulin concentration.

**Analysis of plasma insulin and metabolite concentrations**

Concentrations of insulin in plasma were analysed by RIA using a commercially available kit (Phadeseph Insulin RIA; Pharmacia, Uppsala, Sweden). The intra-assay CV for the insulin assay was 2.7%, and the inter-assay CV was 4.3% (n = 6 assays). Commercially available kits were used to measure concentrations of glucose (GLUC HK; Roche Diagnostic Systems, Basel, Switzerland) and non-esterified fatty acids (NEFA C; Wako Pure Chemical Industries, Tokyo, Japan) in plasma by semi-automated analysis. Intra- and inter-assay CVs for these assays are below 5% in our laboratory. Amino acid concentrations in plasma were analysed colorimetrically as described by Evans et al. [22a]. The intra- and inter-assay CVs were 4.19 and 4.10% respectively for a quality control sample with a concentration of 1.66 mmol of \( \alpha \)-amino nitrogen (n = 4 assays).

**Statistical analyses**

Data were analysed by one-way analysis of variance with treatment group as the factor, followed by \( t \)-tests for specific comparisons of controls with the 27D group and of controls with the 64D group. Insulin secretion data were log-transformed before analysis.

**RESULTS**

After the intravenous administration of a bolus of glucose, plasma glucose levels increased to a maximum of 13.9 ± 1.34 mM in the control group, 11.9 ± 0.49 mM in the 27D group and 12.6 ± 0.84 mM in the 64D group. Glucose tolerance, calculated as the area under the curve, was 427 ± 47 mmol·min⁻¹·kg⁻¹ in the control group, and was not significantly different in either the 27D group (474 ± 25 mmol·min⁻¹·kg⁻¹) or the 64D group (487 ± 34 mmol·min⁻¹·kg⁻¹) (Figure 1a). There were no significant differences in insulin secretion in response to the glucose challenge, corrected for the glucose stimulus experienced, in the two dexamethasone-treated groups (4.6 ± 0.55 and 10.99 ± 4.94 m-units of insulin/mmoll of glucose in the 27D and 64D groups respectively) compared with the controls (4.7 ± 0.87 m-units of insulin/mmoll of glucose) (Figure 1b). The large variation in insulin secretion observed in the 64D group was due to one animal in which insulin secretion was 30.5 m-units of insulin/mmoll of glucose; however, there was no reason to exclude this animal from the statistical analysis.

**Insulin sensitivity**

Basal blood glucose, plasma amino acid nitrogen, plasma non-esterified fatty acids and plasma insulin concentrations did not differ between treatment groups, and are shown in Table 1. The steady-state concentration of insulin, averaged across five samples taken during the final hour of the hyperinsulinaemic euglycaemic clamp, was similar in all treatment groups, and consequently there were no group differences in the metabolic clearance rate of insulin (Table 1).

There were no significant differences in the insulin sensitivity of net whole-body glucose uptake, calculated in terms of the glucose infusion rate required to maintain euglycaemia, in the two dexamethasone treated groups [2.49 ± 0.21 and 2.27 ± 0.21 mg of glucose·kg⁻¹·min⁻¹·m-units/ml insulin]⁻¹ in the 27D and 64D groups respectively] compared with the control group [2.06 ± 0.22 mg of glucose·kg⁻¹·min⁻¹·m-units/ml insulin]⁻¹] (Figure 2a).
Table 1  Effects of prenatal glucocorticoid exposure
The effects of prenatal glucocorticoid exposure on basal plasma glucose, amino acid, non-esterified fatty acid and insulin concentrations, steady-state plasma insulin concentration and the metabolic clearance rate of insulin (MCR) were measured during a hyperinsulinaemic euglycaemic clamp. Values are means ± S.E.M.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>27D group</th>
<th>64D group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal plasma glucose (mM)</td>
<td>3.83 ± 0.12</td>
<td>3.75 ± 0.10</td>
<td>3.65 ± 0.05</td>
</tr>
<tr>
<td>Basal plasma amino acids (mM)</td>
<td>2.15 ± 0.10</td>
<td>2.24 ± 0.12</td>
<td>2.09 ± 0.07</td>
</tr>
<tr>
<td>Basal plasma non-esterified fatty acids (mM)</td>
<td>0.39 ± 0.05</td>
<td>0.52 ± 0.08</td>
<td>0.532 ± 0.077</td>
</tr>
<tr>
<td>Basal plasma insulin (m-units/l)</td>
<td>6.51 ± 0.78</td>
<td>5.99 ± 0.79</td>
<td>5.98 ± 0.49</td>
</tr>
<tr>
<td>Steady-state plasma insulin (m-units/l)</td>
<td>1132 ± 33</td>
<td>1152 ± 20</td>
<td>1091 ± 38</td>
</tr>
<tr>
<td>MCRi (l/min)</td>
<td>5.32 ± 0.15</td>
<td>5.21 ± 0.09</td>
<td>5.33 ± 0.19</td>
</tr>
</tbody>
</table>

The insulin sensitivity of net whole-body amino acid uptake (Figure 2b), measured as the proportional decrease in circulating amino nitrogen concentrations during the hyperinsulinaemic clamp, was 16.3 ± 1.2% in controls, similar to that in the 27D (17.4 ± 1.1%) and the 64D (14.8 ± 2.2%) groups. At steady-state, plasma insulin concentrations were ~ 1000 m-units/l.

However, the suppression of lipolysis by insulin (Figure 2c), measured as the proportional decrease in the circulating concentration of non-esterified fatty acids during the hyperinsulinaemic clamp, differed between treatment groups (P < 0.05). Lipolysis was suppressed by 69 ± 1.2% at steady-state plasma insulin levels (~ 1000 m-units/l) in the 27D group, but by only 50.8 ± 6.5% in the controls. In the 64D group the decrease was 66.4 ± 5.1%, which did not reach significance compared with the controls (P = 0.10).

DISCUSSION

Our hypothesis, i.e. that hypertension found in adult animals that were exposed briefly to dexamethasone at the end of the first month of gestation would not be associated with insulin resistance, proved to be correct. What we had not predicted is that the hypertension in these animals was accompanied by an increased insulin sensitivity of the inhibition of lipolysis. During hyperinsulinaemic euglycaemic clamp studies there was a greater fall in plasma non-esterified fatty acids in the hypertensive group than in the other two groups, which we interpret as being due to inhibition of lipolysis. Regulation of lipolysis and glucose uptake in adipocytes occurs via a common second messenger pathway (reviewed in [23]), suggesting that, in response to a given level of insulin, adipocytes in sheep exposed to dexamethasone in early gestation will take up more glucose and break down less lipid, resulting in increased lipid accumulation. One mechanism by which this may occur is via a down-regulation of β-adrenergic receptors in adipocytes [24], which has been shown to substantially
Table 2  Effects of prenatal glucocorticoid exposure on postnatal function in sheep
Abbreviations: MAP, mean arterial pressure; RAS, renin–angiotensin system.

<table>
<thead>
<tr>
<th>27D group</th>
<th>64D group</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>↑</td>
<td>[18,19]</td>
</tr>
<tr>
<td>Effect of atropine on MAP</td>
<td>←→</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑</td>
<td>←→</td>
</tr>
<tr>
<td>Baroreflex</td>
<td>Shift Rightward</td>
<td>None</td>
</tr>
<tr>
<td>Gain</td>
<td>←→</td>
<td>↓</td>
</tr>
<tr>
<td>Basal plasma RAS</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>RAS during haemorrhage stress</td>
<td>←→</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Glucose uptake</td>
<td>←→</td>
</tr>
<tr>
<td>Amino acid uptake</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>Lipolysis</td>
<td>↓</td>
<td>←→</td>
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</tbody>
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increase the maximal rate of insulin-stimulated glucose transport into rat adipocytes.

Increased adipocyte sensitivity to insulin is a potential mechanism by which increased susceptibility to the development of obesity could develop following exposure to an adverse environment in early gestation. The body composition of the cohort of sheep in the present study has not been characterized, as they are being maintained for further investigation. Thus we do not know if the induction of increased adipocyte sensitivity to insulin by dexamethasone treatment in early gestation has caused obesity in these sheep. Nevertheless, men who were exposed to the Dutch winter famine during the first half of gestation became obese while those exposed during the second half of gestation did not, consistent with our hypothesis [25].

The consequences of prenatal perturbation for the insulin sensitivity of lipolysis have not previously been investigated in vivo. However, in vitro studies in the progeny of rats fed a low-protein diet during pregnancy and lactation have shown that enhanced insulin-sensitivity of adipocytes is observed [26]. Increased levels of insulin receptors in adipocyte membranes, and increased activity of basal and insulin-stimulated phosphatidylinositol 3-kinase activity, were also reported in progeny of rats fed a low-protein diet during pregnancy, lactation, or both pregnancy and lactation [26,27], suggesting a molecular basis for the programming of enhanced insulin-sensitivity of adipocytes during fetal and neonatal life.

Associations between the insulin resistance of glucose metabolism and hypertension in adulthood have been reported in several studies on humans who were small-for-gestational-age at birth [1,28,29]. Further investigation has led to the suggestion that insulin resistance of glucose metabolism is the primary defect in Syndrome X [30,31], and that hypertension is, at least partly, a consequence of impaired vasodilatory actions of insulin in the vascular epithelium [32,33]. In contrast, in our study, fetal steroid exposure at the end of the first month of gestation in sheep resulted in adult sheep which were hypertensive [18,19], but without impaired glucose tolerance, insulin secretion or insulin sensitivity of glucose metabolism (Table 2). Fetal exposure to steroid at the end of the second month of gestation produced adult sheep which were normotensive, but with a decreased baroreflex sensitivity [19], and also without impairments in postnatal glucose homeostasis or in insulin secretion or action (Table 2).

It is possible that it is more difficult to ‘programme’ insulin resistance in sheep than in rats or humans. In sheep most of the glucose available for consumption originates from gluconeogenesis, as little is absorbed from the gut. The ruminant liver has relatively low levels of glucokinase and hexokinase activity, and there is no significant hepatic uptake of glucose; therefore the predominant action of insulin in the liver is to inhibit glucose release [34,35]. It is also known that sheep are more resistant to insulin-induced hypoglycaemic convulsions than are non-ruminants [36]. In addition, the lean sheep is more insulin resistant, in terms of glucose metabolism, than is the lean human, which seems to be due to a post-receptor event [37]. However, insulin resistance can develop during ovine pregnancy, and is exaggerated by undernutrition [38]. Also, ewes whose mothers were undernourished for a 20-day period (105–125 days of gestation) were insulin-resistant by 3 years of age (J. Harding, personal communication).

Hypertension following fetal growth restriction also occurred without impaired insulin sensitivity in rats whose dams were fed a low-protein diet during pregnancy [3,7]. Thus, in our model and some others, hypertension is not linked to impaired insulin sensitivity, and exposure to an adverse fetal environment is able to differentially affect the postnatal function of the car-

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diovascular system and of insulin-regulated glucose homoeostasis.

The presence of hypertension, but not impaired insulin-regulated glucose metabolism, in our model is consistent with these two aspects of postnatal function being susceptible to programming by an adverse fetal environment at different stages of development. The effects of the timing of exposure to prenatal perturbation on postnatal blood pressure have been investigated in progeny of rats whose mothers were fed a low-protein diet for three different periods during gestation. Maternal exposure to low protein for only the first third of gestation resulted in smaller increases in progeny blood pressure than exposure throughout gestation. In male progeny, the increase in blood pressure was similar for animals exposed in each third of gestation; in contrast, in female progeny, blood pressure was increased by exposure during the second or third, but not the first, third of gestation [3]. Treatment of pregnant rats with dexamethasone during the last third of pregnancy also produced hypertension in adult progeny [17]. In a separate study, dexamethasone treatment of pregnant rats in the third, but not in the first or second, week of pregnancy impaired glucose tolerance in the adult progeny [22]. The mechanistic basis for this is unclear, but insulin secretion in the adult offspring was not altered by dexamethasone treatment of the pregnant rat at any stage of gestation [22]. In other studies, a 50% restriction of feed intake in rats during the second half of pregnancy decreased the insulin sensitivity of whole-body glucose uptake and impaired hepatic, but not peripheral, insulin sensitivity in adult female progeny [9,10], while the same level of restriction for the first two-thirds of pregnancy did not alter glucose tolerance, insulin secretion or the insulin sensitivity of whole-body glucose utilization or endogenous glucose production in adult male progeny [8]. Studies in people whose mothers experienced severe nutrient restriction during the Dutch famine found that basal blood pressure was inversely related to birth weight, but was not affected by famine exposure per se, while glucose tolerance was impaired to a greater extent by famine exposure during late gestation than during mid or early gestation [20,21]. However, severe nutrient restriction during the Leningrad famine resulted in only a slight, non-significant, increase in blood pressure, without any effect on glucose tolerance or lipid concentration [39]. The opposing findings for the Dutch and the Leningrad famine studies might be due to different conditions preceding and following the famine periods [21].

In our study, the presence of hypertension or altered baroreflex sensitivity, but not impaired insulin-regulated glucose homoeostasis, in adult female sheep who were exposed to dexamethasone at 27 or 64 days of gestation is consistent with susceptibility of blood pressure regulation, but not of postnatal glucose metabolism or insulin secretion or action, to programming by an adverse fetal environment during early to mid gestation. It is not known whether glucocorticoid exposure later in gestation affects the postnatal regulation of both hypertension and glucose metabolism through a common mechanism, such as impaired insulin sensitivity.

In conclusion, steroid exposure during early gestation programmed hypertension independently of the insulin resistance of glucose or amino acid metabolism, suggesting that programming of hypertension and insulin resistance can involve different mechanisms and occurs at different stages of development. Insulin sensitivity of the inhibition of lipolysis was increased by dexamethasone exposure at 27 days of gestation. We speculate that this represents a potential mechanism by which susceptibility to the development of obesity could result postnatally following exposure to an adverse fetal environment in early gestation.

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