Maternal Semistarvation and Streptozotocin-Diabetes in Rats Have Different Effects on the In Vivo Glucose Uptake by Peripheral Tissues in Their Female Adult Offspring

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ABSTRACT Previous work in humans and rats has revealed a link between perinatal growth retardation and glucose intolerance in adulthood. Both maternal semistarvation and severe diabetes are accompanied by perinatal growth retardation in rats. In this study, we compared the effects of these conditions on tissue glucose uptake in their female offspring. Glucose uptake was measured as glucose metabolic index (GMI), using 2-deoxy-[1-3H]-glucose, in the postabsorptive state and during euglycemic hyperinsulinemia. The GMI was measured in insulin-sensitive tissues (5 skeletal muscles, diaphragm and white adipose tissue) and in two noninsulin-sensitive tissues (duodenum and brain) of adult offspring of normal dams, dams rendered diabetic with streptozotocin on day 11 of pregnancy, and dams fed half normal rations from day 11 of pregnancy. Whole-body insulin resistance, measured by decreased glucose infusion rate during hyperinsulinemia, was milder in offspring of semistarved rats (O-SR) than in offspring of diabetic rats (O-DR). The basal GMI did not differ among the three groups in any tissue except tibialis anterior; during hyperinsulinemia, GMI was significantly greater in the insulin-sensitive tissues of all three groups. GMI of skeletal muscles and adipose tissue during hyperinsulinemia did not differ between control rats and O-SR; in contrast, the GMI was 25–50% lower in skeletal muscles of O-DR during hyperinsulinemia than in those of control rats or O-SR. Thus, maternal semistarvation and diabetes have dissimilar effects on peripheral insulin sensitivity of the adult female offspring. Because both conditions are associated with perinatal growth retardation and fetal hypoinsulinemia, other mechanisms must be identified to explain impaired glucose uptake by skeletal muscles in the offspring of diabetic rats. J. Nutr. 127: 1371–1376, 1997.

KEY WORDS: • diabetes • semistarvation • adult offspring • peripheral glucose uptake • rats

There is accumulating evidence in humans that low birth weight, and more specifically thinness at birth, is accompanied by an increased risk of impaired glucose tolerance and noninsulin-dependent diabetes mellitus (NIDDM) in adulthood (Phipps et al. 1993). This epidemiological association would imply that a restriction of the in utero growth potential induces insulin resistance (Phillips 1996).

In a rat model, we have produced evidence that the adult offspring of semistarved dams show insulin resistance in the liver (i.e., there is less inhibition of glucose production during euglycemic hyperinsulinemia) but apparently not in the peripheral tissues (Holemans et al. 1996). The adult offspring of severely diabetic rats, on the other hand, exhibit insulin resistance that involves both hepatic glucose production and glucose uptake by skeletal muscles (Holemans et al. 1991a and 1993, Ryan et al. 1995). We obtained a comparable degree of growth retardation during the perinatal period under both conditions (Holemans et al. 1991a and 1996), which is the result of a reduction in uteroplacental blood flow during pregnancy (Eriksson and Jansson 1984, Rosso and Kava 1980) and a decreased milk volume during lactation (Ikawa et al. 1992, Rasmussen and Warman 1983).

Skeletal muscles represent the main reservoir of insulin-sensitive tissues within the mammalian body, equivalent to about 40% of total body weight (Knopp et al. 1970). In anesthetized rats, the contribution of skeletal muscles to the whole-body glucose turnover rate is about 36% in the postabsorptive state and 50% during euglycemic hyperinsulinemia (Ferré et al. 1985). In humans, 70–75% of glucose is removed by skeletal muscles during euglycemic hyperinsulinemia (DeFronzo et al. 1981); in contrast, adipose tissue contributes only about 3% to the glucose disposal after an oral glucose tolerance test (Marin et al. 1987). Impaired glucose uptake by skeletal muscles is estimated to account for about 80% of whole-body insulin resistance in NIDDM subjects (Bonadonna et al. 1993).

In this study, we compared the long-term effects of perinatal growth retardation, caused by maternal semistarvation or diabetes, on the glucose uptake by skeletal muscles and adipose tissue in adulthood. We reasoned that a direct comparison of growth retardation during the perinatal period under both conditions (Holemans et al. 1991a and 1996), which is the result of a reduction in uteroplacental blood flow during pregnancy (Eriksson and Jansson 1984, Rosso and Kava 1980) and a decreased milk volume during lactation (Ikawa et al. 1992, Rasmussen and Warman 1983).

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3 Abbreviations used: GMI, glucose metabolic index; 2-[3H]D-G, 2-deoxy-[1-3H]-glucose; NIDDM, noninsulin-dependent diabetes mellitus; O-DR, offspring of diabetic rats; O-SR, offspring of semistarved rats.
between the conditions could reveal whether the quantitative restriction in maternal-fetal/neonatal nutrient transfer, present in semistarvation and diabetes, is crucial to the induction of peripheral insulin resistance; if not, then other mechanisms must be involved. Semistarvation and diabetes were present during the same developmental period, i.e., from d 11 of fetal life until weaning. Because the insulin sensitivity in skeletal muscles in mammals is determined by its fiber-type composition (Bonen et al. 1981), we studied several types of muscle, including slow-twitch oxidative (soleus and adductor longus muscles), fast-twitch oxidative glycolytic (epitrochlearis) and fast-twitch glycolytic (extensor digitorum longus and tibialis anterior) (Ariano et al. 1973, Armstrong and Phelps 1984, Nesher et al. 1980).

MATERIALS AND METHODS

Animals. The study protocol was reviewed and approved by the local ethics committee. Maternal rats were control pregnant Wistar rats, diabetic pregnant rats and semistarved pregnant rats (Leuven/ pfd, K.U.Leuven Breeding Center, Leuven, Belgium). Diabetes mellitus was induced experimentally by a single intravenous injection of streptozotocin (35 mg/kg body weight; Upjohn, Puurs, Belgium) on d 11 of pregnancy (d 1 was the day of the copulation plug). The semistarved maternal rats received 11 g/d of a nonpurified diet from d 11 of pregnancy until the day of delivery (d 23), and 20 g/d of the same diet during the entire lactation period. This food restriction scheme ensured that the maternal rats received about 50% of the ad libitum food intake (Aerts et al. 1990, Cole and Hart 1938). The diet was a standard nonpurified diet (Trouw, Gent, Belgium) with an approximate composition of 21% protein, 4% fat, 51% carbohydrate, 7% ash, 5% cellulose and 12% water. All rats had free access to tap water. The pregnant rats were weighed on d 20, and a tail blood sample was obtained for measurement of plasma glucose, insulin concentrations. On d 22 of pregnancy, a first subgroup of pregnant rats was anesthetized with pentobarbital (0.24 mmol/kg, intraperitoneal), and blood was collected from their fetuses via an axillary incision; only the offspring of rats with eight or more fetuses were included in the study. A second subgroup of pregnant rats was allowed to deliver spontaneously and to nurse their pups in standard laboratory conditions. After weaning, the female offspring of rats with eight or more pups were kept for the purpose of this study. The offspring had free access to food and water. At 100 d of age, they were weighed and a tail blood sample was obtained. When the rats were between 100 and 120 d of age, the glucose metabolic index was determined.

In a second group, comprised of normal rats and offspring of semistarved rats (O-SR) and diabetic rats (O-DR), the female offspring were weighed on 14, 21, 28, 35, 42, 49, 70 and 91 d postnatally. When rats were ~100 d of age, daily food and water intake was measured in the three groups.

Euglycemic hyperinsulinemic clamp. Food was withheld for 3 h before starting the experiment. Rats were anesthetized with pentobarbital (0.24 mmol/kg, intraperitoneal), the right carotid artery was catheterized for blood sampling, and a tracheotomy was performed. Body temperature was maintained at 38°C with a heating lamp and a heating blanket.

The clamp studies were performed exactly as described previously (Holemans et al. 1991a). On the basis of our previous data (Holemans et al. 1991a and 1996), different doses of insulin (porcine monocomponent insulin, Novo Industri, Bagsvaerd, Denmark) were infused in a saphenous vein at a constant rate (20 µL/min) in the offspring of control rats and semistarved rats [0.06 mmol/kg (kg · min)], and in the offspring of diabetic rats [0.04 mmol/kg (kg · min)] to obtain steady-state plasma insulin concentrations of ~2.0 mmol/L in all rats.

Measurement of the glucose metabolic index in individual tissues. The glucose metabolic index (GMI) was determined as previously described (Holemans et al. 1993). In the basal state, 1.11 MBq of 2-[3H]D-glucose (2-[3H]D-G; Amersham International, Buckinghamshire, UK) dissolved in 200 µL of 9 g/L NaCl was given as a bolus in the saphenous vein 30 min after surgery. Arterial blood (50 µL) was sampled at 1, 3, 5, 10, 20, 30, 45 and 60 min. The clamp studies were started 30 min after surgery. When steady-state was reached, 1.11 MBq of 2-[3H]D-G in 200 µL of 9 g/L NaCl was given as a bolus via the saphenous vein. Arterial blood (50 µL) was taken at the start and at the end of each experiment for the measurement of plasma insulin by RIA using rat and porcine insulin standards, respectively (Novo Industri). After the last blood sample, rats were killed by cervical dislocation, and five skeletal muscles (soleus, adductor longus, epitrochlearis, extensor digitorum longus and tibialis anterior muscles), diaphragm, pieces of perivascular white adipose tissue, both cerebral hemispheres, and pieces of duodenum were rapidly removed within 5 min. The tissues were placed in 0.5 mL of 1 mol/L NaOH, digested at 60°C (45 min) and neutralized with 1 mol/L HCl. Neutralized solution (200 µL) was added to 1 mL of 0.6 mol/L HClO₄, and 200 µL was added to 0.5 mL of 85 mmol/L Ba(OH)₂, and 200 µL of 85 mmol/L ZnSO₄. After centrifugation at 5000 × g for 2 min, samples of both supernatants were counted in a Packard liquid scintillation counter (Packard Instruments, Canberra, Australia). A larger blood sample (200 µL) was taken at the start and the end of each experiment for the determination of blood glucose concentration by the d-glucose oxidase-d-peroxidase method (GOD-PAP, Boehringer Mannheim, Mannheim, Germany). Another aliquot was used to count 2-[3H]D-G in the liquid scintillation counter (Packard Instruments, Canberra, Australia). A large blood sample (500 µL) was taken at the start and the end of each experiment for the determination of blood glucose concentration by the d-glucose oxidase-d-peroxidase method (GOD-PAP, Boehringer Mannheim, Mannheim, Germany). Another aliquot was used to count 2-[3H]D-G in the liquid scintillation counter (Packard Instruments, Canberra, Australia).

Calculations and statistical analysis. The GMI for each tissue was calculated by dividing the amount of 2-deoxy-[1-3H]glucose-6-phosphate in the tissue by the calculated integral of the ratio of arterial blood 2-[3H]D-G to glucose concentration (Kraegen et al. 1985). Data are presented as means ± SEM. Intergroup differences were analyzed by one-way ANOVA. When variances were unequal, ANOVA was performed on randomly selected samples of equal sizes from each group (Dawson-Saunders and Trapp 1990). When the F-test was significant (P < 0.05), unpaired t tests were used to compare pairs of means. Differences between basal and hyperinsulinemic conditions were analyzed by two-way ANOVA. When the F-test was significant (P < 0.05), paired t tests were used to compare pairs of means.

RESULTS

General features. Pregnant rats injected with streptozotocin were severely hyperglycemic, hypoinsulinemic but they maintained a normal body weight (Table 1). Pregnant rats fed half-normal rations were relatively hypoglycemic, hypoinsulinemic and had a lower body weight compared with control rats. On d 22 of pregnancy (the day before birth), fetuses of diabetic rats were severely hyperglycemic, whereas fetuses of semistarved rats were hypoglycemic (Table 2). In both groups, the fetuses were hypoinsulinemic and had lower body weights. The 100-d-old offspring of both diabetic rats (O-DR, previously termed SDF rats by us (Holemans et al. 1991a) and se-

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Semistarved</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>288 ± 3</td>
<td>257 ± 4a</td>
<td>292 ± 6c</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.44 ± 0.22</td>
<td>3.61 ± 0.11b</td>
<td>26.8 ± 1.3a,c</td>
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<tr>
<td>Insulin, nmol/L</td>
<td>0.34 ± 0.04</td>
<td>0.17 ± 0.03b</td>
<td>0.11 ± 0.07a</td>
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</tbody>
</table>

1 Values are means ± SEM. a P < 0.001, b P < 0.01, vs. control group; c P < 0.001 vs. the semistarved group.
mistarved rats (O- SR) had lower body weights than controls (Table 3). In O-DR, glucose levels were within the normal range, whereas insulin concentrations were greater than in controls. Glucose concentrations were 18% higher in O- SR rats than in control rats, whereas insulin concentrations were lower than in control rats (P < 0.05).

**Weight gain and food intake in offspring of control, semistarved and diabetic rats.** Postnatally, body weights in O- SR and O-DR increased in parallel with body weight in control rats, but there was no catch-up growth (Fig. 1). At each time point, body weights in O- SR and O-DR were significantly lower than in control rats (P < 0.001). Absolute daily food intakes were lower in O- SR and O-DR than in control rats (Table 4). However, when food intake was expressed relative to body weight, groups did not differ significantly (Table 4). Absolute water intake was lower in O- DR than in control rats or O- SR.

**Euglycemic hyperinsulinemic clamp.** To obtain the same hyperinsulinemic plateau (about 2 nmol/L) in control rats, the insulin infusion rate was 0.06 mmol/(kg·min); the insulin infusion rate was 0.06 mmol/(kg·min) in both control rats and O- SR, and 0.04 mmol/(kg·min) in O-DR. The glucose infusion rate necessary to maintain euglycemia (Table 5) was significantly lower in both O-DR and O- SR compared with control, and was lower in O-DR than in O- SR (P < 0.05; Table 5). Under basal conditions and during hyperinsulinemia, 2-[3H]D-G specific activity at 60 and 45 min was about 10% of the initial 2-[3H]D-G specific activity (data not shown).

**Glucose metabolic index in individual tissues.** Offspring of semistarved rats vs. control rats. The basal GMI of the various tissues studied (Fig. 2) were not altered in O- SR. The GMI of the skeletal muscles (Fig. 2A), diaphragm and white adipose tissue (Fig. 2B), but not brain and duodenum (Fig. 2B), in O- SR were stimulated by hyperinsulinemia to the same extent as in control rats (both P < 0.001), and no differences were observed between control rats and O- SR during euglycemic hyperinsulinemia.

Offspring of diabetic rats vs. control rats. Under basal conditions, only the GMI of the tibialis anterior muscle was lower in O-DR than in controls (P < 0.05; Fig. 2A). Hyperinsulinemia increased the GMI of the skeletal muscles, diaphragm and white adipose tissue in control rats (P < 0.001) and O-DR (P < 0.01). However, during hyperinsulinemia, the GMI of all five skeletal muscles was consistently 25–50% lower in O-DR than in controls; in contrast, the GMI of diaphragm was not significantly different between control rats and O- DR. The GMI in white adipose tissue of O-DR at hyperinsulinemia tended to be higher than in controls (P = 0.07; Fig. 2B).

Offspring of semistarved rats vs. offspring of diabetic rats. In the basal state, the GMI of the tibialis anterior muscle was significantly lower in O- DR than in O- SR (P < 0.05; Fig. 2A), but the GMI of all other tissues did not differ between the two groups. During euglycemic hyperinsulinemia, the GMI of all skeletal muscles of O- DR was lower than in those of O- SR (Fig. 2A). The GMI of white adipose tissue was higher in O-DR than in O- SR (P < 0.02), whereas that of the diaphragm did not differ between the two groups (Fig. 2B).

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**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Semistarved</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>5.11 ± 0.05</td>
<td>4.07 ± 0.05c</td>
<td>4.23 ± 0.04c</td>
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<tr>
<td>Glucose, mmol/L</td>
<td>3.68 ± 0.12</td>
<td>2.77 ± 0.08b</td>
<td>20.4 ± 0.54d</td>
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<tr>
<td>Insulin, mmol/L</td>
<td>1.59 ± 0.12</td>
<td>0.77 ± 0.07c</td>
<td>0.87 ± 0.03c</td>
</tr>
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</table>

1 Values are means ± SEM. 2 Number of fetuses analyzed in parentheses.

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**TABLE 3**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>O-SR</th>
<th>O-DR</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>23</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>209 ± 3</td>
<td>181 ± 4a</td>
<td>184 ± 2a</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.61 ± 0.17</td>
<td>6.66 ± 0.2a</td>
<td>5.43 ± 0.22c</td>
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<tr>
<td>Insulin, mmol/L</td>
<td>0.17 ± 0.01</td>
<td>0.14 ± 0.01b</td>
<td>0.21 ± 0.02c</td>
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</table>

1 Values are means ± SEM. 2 P < 0.001, bP < 0.05 vs. control group; cP < 0.001 vs. semistarved group.

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**TABLE 4**

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<tr>
<th></th>
<th>Control</th>
<th>O-SR</th>
<th>O-DR</th>
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<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Food intake, g/d</td>
<td>16.6 ± 0.4</td>
<td>13.8 ± 0.6a</td>
<td>13.1 ± 0.5a</td>
</tr>
<tr>
<td>g/(kg·d)</td>
<td>95 ± 3</td>
<td>101 ± 5</td>
<td>92 ± 3</td>
</tr>
<tr>
<td>Water intake, mL/d</td>
<td>31 ± 2</td>
<td>29 ± 2</td>
<td>24 ± 1a</td>
</tr>
<tr>
<td>mL/(kg·d)</td>
<td>179 ± 11</td>
<td>215 ± 12b</td>
<td>170 ± 9c</td>
</tr>
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1 Values are means ± SEM. 2P < 0.01, bP < 0.05 vs. control group; cP < 0.05 vs. semistarved group.
Plasma insulin, glucose concentrations and steady-state glucose infusion rate in female adult offspring of control, semistarved (O-SR) and diabetic (O-DR) rats under basal conditions and during euglycemic hyperinsulinemia.

<table>
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<th>Plasma insulin</th>
<th>Blood glucose</th>
<th>Glucose infusion rate</th>
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<tr>
<td></td>
<td>n</td>
<td>Basal (nmol/L)</td>
<td>Clamp (nmol/L)</td>
</tr>
<tr>
<td>Control</td>
<td>10</td>
<td>0.17 ± 0.02</td>
<td>2.17 ± 0.22&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>O-SR</td>
<td>10</td>
<td>0.19 ± 0.02</td>
<td>1.75 ± 0.30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>O-DR</td>
<td>9</td>
<td>0.21 ± 0.02</td>
<td>1.91 ± 0.18&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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1 Values are means ± SEM. aP < 0.001 vs. basal conditions; bP < 0.01; cP < 0.01, vs. control group; dP < 0.05 vs. offspring of semistarved rats.

**DISCUSSION**

This study compared the effects of maternal semistarvation and diabetes, from d 11 of pregnancy until weaning, on tissue glucose uptake and plasma insulin concentrations in their female adult offspring, and the data show that the effects are dissimilar. In both semistarved and diabetic dams, perinatal growth is stunted by decreased uteroplacental blood flow (Eriksson and Jansson 1984, Rosso and Kava 1980) and milk volume (Ikawa et al. 1992, Rasmussen and Warman 1983). In both models of perinatal growth retardation, we observed 20% lower body weights in 22-d-old fetuses. Postnatally, body weight increased parallel to that of control rats, but there was no catch-up growth; thus, perinatal growth retardation has a long-lasting effect on body weight. This is in agreement with another study in which a similar food restriction scheme was used (Woodall et al. 1996). Moreover, food intake at 100 d of age, when expressed relative to body weight, was normal in both groups. Although semistarvation during the perinatal period had no effect on the glucose uptake by skeletal muscles and adipose tissue in the adult offspring, diabetes consistently reduced glucose uptake by five skeletal muscles; the latter finding confirms our previous study (Holemans et al. 1993). The present results also confirm and extend our previous calcula-
tions of the glucose utilization rate in these conditions during euglycemic hyperinsulinemia (Holemans et al. 1991a and 1996). In addition, because skeletal muscles represent the bulk of insulin-responsive tissues, whole-body insulin resistance, measured by the steady-state glucose infusions rate during hyperinsulinemia (Table 5), was more pronounced in O-DR than in O-SR. Insulin resistance in O-DR probably represents a post-binding defect, because we found that the insulin binding in liver plasma membranes and in adipocytes was not decreased in O-DR (Holemans 1993). The defect in peripheral glucose uptake in O-DR was accompanied by higher plasma insulin concentrations, as we have reported previously (Holemans et al. 1991a and 1993). This relative hyperinsulinemia reflects the higher insulin secretion by pancreatic B cells of O-DR, which we have documented both during an intravenous glucose tolerance test (Van Assche and Aerts 1986) and in vitro in isolated islets (Aerts et al. 1988); in turn, the stimulation of insulin secretion in O-DR is presumably the consequence of peripheral and hepatic insulin resistance. Under basal conditions, O-DR maintain normoglycemia (Table 3; Holemans et al. 1991a, 1991b and 1993). During pregnancy, however, the increase in plasma insulin levels in O-DR is less than in control rats, and relative hyperglycemia (i.e., “gestational diabetes”) ensues (Holemans et al. 1991b).

O-SR, on the other hand, had a milder degree of insulin resistance (Table 5), which was confined to the liver (Holemans et al. 1996). In addition, their plasma insulin concentrations were lower than those of control rats, confirming our previous data (Holemans et al. 1996), whereas their glucose levels were slightly, and significantly, higher. Interestingly, we
found that such relative hyperglycemia was present only if O-SR had been subjected to undernutrition during both fetal and neonatal life (Holemans et al. 1996). Thus, the primary defect in glucose regulation in O-SR appears to be at the endocrine pancreas, and the in vitro insulin secretion in O-SR will be further studied. Indeed, the mild insulin resistance of the liver in O-SR rats may well be the result of hypoinsulinemia itself, as has been shown in mildly diabetic rats subjected to long-term undernutrition (Rao and Menon 1993).

What have we learned from these experiments about the mechanisms by which insulin resistance is induced in O-DR and the time period in which it occurs? First, we have found that the adult body weight of O-DR is not in itself the cause of whole-body insulin resistance (Holemans et al. 1991a) or decreased peripheral glucose uptake (these experiments). Second, perinatal growth retardation is not the cause of peripheral insulin resistance in O-DR because O-SR and O-DR had comparable degrees of restriction of growth potential during fetal and neonatal life. Third, peripheral insulin resistance is not caused by hypoinsulinemia during fetal—and, probably, neonatal life because fetal insulin concentrations on d 22 were similarly decreased as a result of semistarvation and diabetes. It must be added, though, that the effects of maternal undernutrition and diabetes on the morphology of the fetal endocrine pancreas differ: fetal hypoinsulinemia in maternal malnutrition is the result of lower B cell mass, as shown in other models of intrauterine growth retardation (Dhari et al. 1991, De Prins and Van Assche 1982), whereas fetal hypoinsulinemia in severe maternal diabetes (Kervran et al. 1978) is accompanied by overstimulated and exhausted fetal pancreatic B cells on electronic microscopy (Aerts and Van Assche 1977). Clearly, what is different in the perinatal development of both groups is hypoglycemia (O-SR) or hyperglycemia (O-DR). Therefore, the effects of maternal diabetes and hyperglycemia induced by an intravenous glucose infusion on insulin receptor binding and post-binding events must be further examined, both in their fetuses and in their postnatal offspring. The post-binding events include the following: insulin receptor tyrosine kinase activity, concentrations of intracellular glucose transporters and intracellular enzymatic defects in glucose metabolism. Recently, it has been reported that fetuses of diabetic rats have decreased levels of the glucose transporter GLUT1 in their skeletal muscles (Schroeder et al. 1997).

In this study, diabetes was induced on d 11 of pregnancy, but the effects on whole-body insulin resistance and peripheral glucose uptake in the adult offspring were similar to those observed when diabetes was induced on d 1 of pregnancy (Holemans et al. 1993). Thus, the effects of maternal diabetes on insulin sensitivity in the offspring must be induced either during the second half of fetal life or during neonatal life. If we extrapolate our data obtained in O-SR to the situation in O-DR, it would seem that the second half of fetal life is the crucial period: indeed, O-DR had a similar degree of whole-body insulin resistance regardless of whether their dams were semistarved during the second half of pregnancy alone or during both that period and lactation (Holemans et al. 1996).

Finally, toxic effects of streptozotocin on the fetal endocrine pancreas can be excluded for the following reasons: 1) streptozotocin has a very short (30 min) half-life (Schein and Loftus 1968); 2) the differentiation of the endocrine pancreas does not occur before d 15 of gestation (Pictet and Rutter 1972); 3) streptozotocin has no cytotoxic effect on fetal pro-islets (Liu et al. 1994); and 4) the insulin resistance in O-DR occurs irrespective of the time of streptozotocin injection, i.e., either before mating (Ryan et al. 1995), on d 1 of pregnancy (Holemans et al. 1993) or on d 11 of pregnancy (this study).

LITERATURE CITED


