Fetal Physiological Programming

Islet cell response in the neonatal rat after exposure to a high-fat diet during pregnancy

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Cerf, M. E., K. Williams, X. I. Nkomo, C. J. Muller, D. F. Du Toit, J. Louw, and S. A. Wolfe-Coote. Islet cell response in the neonatal rat after exposure to a high-fat diet during pregnancy. Am J Physiol Regul Integr Comp Physiol 288: R1122–R1128, 2005. First published February 10, 2005; doi:10.1152/ajpregu.00335.2004.—Although pancreatic β-cells are capable of adapting their mass in response to insulin requirements, evidence has shown that a dietary insult could compromise this ability. Fetal malnutrition has been linked to low birth weight and the development of type 2 diabetes later in life, while reduced β-cell mass has been reported in adults fed a high-fat diet (HFD). Reported here are the effects of exposure to a HFD, during different periods of gestation, on neonatal rat weight and islet cell development. The experimental groups were composed of neonatal offspring obtained from Wistar rats fed a high-fat (40% as energy) diet for either the first (HF1), second (HF2), or third (HF3) week, or all three (HF1–3) weeks of gestation. Neonatal weights and circulating glucose and insulin concentrations were measured on postnatal day 1, after which the pancreata were excised and processed for histological immunocytochemical examination and image analysis. HF1 and HF2 neonates were hypoglycemic, whereas HF1–3 neonates were hyperglycemic. Low birth weights were observed only in HF1 neonates. No significant differences were detected in the circulating insulin concentrations in the neonates, although β-cell volume and numbers were reduced in HF1–3 neonates. β-cell numbers also declined in HF1 and HF3 neonates, α-cell volume, number and size were, however, increased in HF1–3 neonates. α-cell size was also increased in HF1 and HF3 neonates. In neonates, exposure to a maternal HFD throughout gestation was found to have the most adverse effect on β-cell development and resulted in hyperglycemia.

α-cell; β-cell; in utero programming

Islet cells are believed to originate from pluripotent progenitor cells both during development and later in life (36). Islet progenitor cells arise from the pancreatic ductal epithelium and undergo a series of cytodifferentiation steps that lead to the formation of mature islets (2). Endocrine cell buds develop from duct epithelium (46), and most new β-cells are formed by neogenesis during late fetal gestation (16, 29, 50) and early neonatal life (10, 52). In the rat, the various endocrine cell types appear independently during different times of gestation (46). The size and number of islets continue to increase as the animal develops, with continued growth of each islet cell population throughout the prenatal and postnatal development of the rat (29, 46).

The thrifty phenotype hypothesis states that malnutrition in utero causes β-cell development to be irreversibly damaged by inadequate nutrition during critical periods of fetal development (25). Epidemiological studies, using archival records of measurements related to human fetal growth, have shown strong statistical links between birth weight and/or maternal nutrition and type 2 diabetes, and the insulin resistance syndrome in adult life (25). It has been hypothesized that these associations involve adaptive alterations of fetal organogenesis in response to maternal and, indirectly, fetal nutrition. Poor nutrition in utero, followed by normal or supranormal nutrition after birth can result in impaired growth of β-cells and a predisposition of the individual to develop type 2 diabetes later in life (25). This was supported by the finding that intrauterine low-protein exposure, in rats, reduces pancreatic islet size, islet vascularization, number of β-cells and insulin content (6, 48).

A HFD has been shown to be linked to the development of obesity, insulin resistance, and type 2 diabetes, as well as the impairment of the glucose-signaling system in the β-cell, thereby suppressing insulin secretion (30, 31, 53). Exposure to a HFD in utero could metabolically program the fetus to adapt to the HFD at this critical time of development. We have previously shown a reduction in β-cell volume in adult Vervet monkeys, after maintenance on a HFD for 18 mo (40). A reduction in β-cell mass, with increased apoptosis relative to proliferating β-cells, at 20 and 30 wk of age, has been reported in mice maintained on a high-fat/high-protein diet or a HFD (39). The aim of this study was to investigate the changes that occur in neonatal rat islet cell development, particularly in the β-cell, after exposure to a HFD during specific periods of gestation.

MATERIALS AND METHODS

Experimental groups. All animal experiments were approved by the Ethics Committee of the Medical Research Council (MRC) in South Africa and rigorously adhered to National Institutes of Health ethical guidelines for the care and use of laboratory animals. Wistar rats were housed individually with free access to food and water at the MRC Primate Unit (Cape Town, South Africa). The room was maintained at a temperature of 24°C with a 12:12-h light-dark cycle.

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Pregnant rats were fed a HFD for the first (HF1 dams), second (HF2), or third (HF3) week, or for all three (HF1–3) weeks of gestation. After delivery, neonates were obtained from each group of dams to assess islet cell development. The individual neonatal groups were therefore exposed to a maternal HFD during the first (HF1 neonates), second (HF2), or third (HF3) week, or all three (HF1–3) weeks of gestation. The control groups comprised dams, maintained on a standard laboratory diet, and their offspring. The standard laboratory diet comprised 10% fat, 15% protein, and 75% carbohydrate as energy (2.6 kcal/g), whereas the HFD contained 40% fat, 14% protein and 46% carbohydrate (2.06 kcal/g).

**Determination of circulating glucose and insulin concentrations.**
Maternal food intake, body weight, and circulating glucose and insulin concentrations were monitored during pregnancy. Dams were fasted for 3 h, and blood was collected from the tail vein before pregnancy, on days 7 and 14 of pregnancy and after delivery. Rats were anesthetized using an anesthetic machine (Motivus Resuscitator Type AV, Crest Healthcare Technology, Johannesburg, South Africa) with fluothane (Halothane, AstraZeneca Pharmaceuticals, Johannesburg, South Africa) and 2% oxygen. After the rat was anesthetized, the tip of the tail was heated with a UV lamp to facilitate blood flow, then snipped with a surgical blade. The blood glucose and serum insulin concentrations were determined for the neonates, as described below.

On postnatal day 1, neonates were weighed, and blood glucose concentrations were determined using a glucometer (Precision QID, MediSense, Oxfordshire, UK). To determine the serum insulin concentrations, blood was collected in tubes and placed on ice before centrifugation (Biofuge 13, Heraeus Sepatech, Osterode am Harz, Germany) at 13,000 rpm for 10 min at RT. The clear serum supernatant was collected, and insulin concentrations were determined using a Rat Insulin RIA KIT (Linco Research, St. Charles, MO).

**Tissue preparation and sectioning.**
Pancreas, excised from one-day-old neonatal rats, was placed in 4% paraformaldehyde overnight and processed in an automated tissue processor (Shandon Citadel 1000, Cheshire, UK) through ascending concentrations of ethanol from 70–100%, followed by xylenes. The tissue was embedded in paraffin wax (Paraplast Plus, Monocryl Scientific, St. Louis, MO). Sections, 4 μm thick, were cut on a rotary microtome and mounted on slides coated with 3-aminopropyltriethoxysilane. For histological examination, one slide per neonate was placed in an oven at 60°C for 30 min, dewaxed with xylene, and rehydrated through a descending series of ethanol. Sections stained with hematoxylin and eosin were examined for morphological changes.

Serial sections were incubated for 5 min in 0.228% periodic acid to inhibit endogenous peroxidases. Alpha-cells, in each section, were immunolabeled first, using a polyclonal glucagon antibody (Dako, Carpinteria, CA) and processed in an automated tissue processor (Shandon Citadel 1000, Cheshire, UK) for 30 min at room temperature followed by 0.05% diaminobenzidine tetrahydrochloride. Beta-cells were then labeled by a monoclonal insulin antibody, overnight at 4°C, (Sigma Immunochemicals, St. Louis, MO) followed by avidin-biotin-peroxidase complex (Vectastain, Burlingame, CA). Fuchsin (Dako, Carpinteria, CA) was used to reveal the immunolabeled insulin-secreting β-cells. In the method controls, primary antibody was omitted. All sections were counterstained with hematoxylin.

**Image analysis.** A Canon Powershot S40 digital camera (Tochigi, Japan) mounted on an Olympus BX60 light microscope (Tokyo, Japan) attached to a personal computer was used to capture images. The camera focus, light intensity, and image resolution were controlled remotely, and the acquired images were transferred to the computer using remote capture software from Canon. An islet was defined as a group of eight or more endocrine cells. Image analysis was performed with the Leica Qwin Plus Software (Cambridge, UK).

For each pancreas, one section was cut and immunostained for image analysis. The entire section was viewed using a ×10 objective, and each alternative field of view captured and digitized to 768 × 1,024 pixels. Image analysis was performed on each of the captured images. Tissue parameters were measured using either the interactive option or color segmentation. Total tissue area was determined by adding the tissue measured in each field of view using the interactive measurement option of the Leica Software. Total islet, α-cell and β-cell areas were determined by using color segmentation and thresholding. The relative β-cell volume was calculated as the ratio of the measured area of immunoreactive β-cells to the total area of islet cells. Beta-cell number was assessed by counting the number of β-cell nuclei. In instances where a field of view had an islet, the β-cell number was assessed by counting the number of nuclei in insulin-positive cells. The sum of all the β-cells counted was calculated to determine the number of β-cells per section. Beta-cell size was calculated by dividing the measured β-cell area by the number of β-cell nuclei counted and expressed in squared micrometers. Alpha-cell volume, number, and size were calculated in a similar manner. The β-cell to α-cell ratio (β-cell/α-cell) was determined by dividing the total β-cell area measured by the total α-cell area measured.

**Statistical analysis.** The data of each group were compared with the control data and reported as means ± SE. Comparisons between the groups were analyzed using the one-way ANOVA followed by Bonferroni’s multiple comparisons for significance tests. Significance was established at P < 0.05.

**RESULTS**

**Maternal food consumption and body weight.** Dams fed a HFD for any single week of gestation ingested more food in that week than in the weeks that they were maintained on a standard laboratory diet (Table 1). HF2, HF3, and HF1–3 dams consumed significantly more food during the 21 days of gestation than the control dams. There were no significant differences between the weights of virgin Wistar rats before they were mated (Table 1). At days 7 and 14 of gestation and after

### Table 1. Maternal food consumption and body weight during pregnancy

<table>
<thead>
<tr>
<th>Food intake from day 1 to day 7 of pregnancy, g</th>
<th>Control</th>
<th>HF1</th>
<th>HF2</th>
<th>HF3</th>
<th>HF1–3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake from day 1 to day 7 of pregnancy, g</td>
<td>19.47 ± 0.38</td>
<td>28.26 ± 0.42*</td>
<td>19.82 ± 0.85</td>
<td>17.79 ± 0.23</td>
<td>29.42 ± 0.91*</td>
</tr>
<tr>
<td>Food intake from day 8 to day 14 of pregnancy, g</td>
<td>19.32 ± 0.69</td>
<td>17.54 ± 1.54</td>
<td>29.4 ± 1.19*</td>
<td>21.16 ± 0.74</td>
<td>30.06 ± 0.96*</td>
</tr>
<tr>
<td>Food intake from day 15 to day 21 of pregnancy, g</td>
<td>21.72 ± 0.89</td>
<td>21.62 ± 1.56</td>
<td>21.25 ± 1.07</td>
<td>30.91 ± 1.41*</td>
<td>28.39 ± 0.99*</td>
</tr>
<tr>
<td>Overall food intake throughout pregnancy, g</td>
<td>20.17 ± 0.45</td>
<td>22.47 ± 1.12</td>
<td>23.49 ± 1.10*</td>
<td>23.29 ± 1.35*</td>
<td>29.29 ± 0.55*</td>
</tr>
<tr>
<td>Maternal weight before pregnancy, g</td>
<td>203.9 ± 3.46</td>
<td>210.6 ± 3.93</td>
<td>211.8 ± 3.61</td>
<td>197.7 ± 4.17</td>
<td>204.3 ± 4.91</td>
</tr>
<tr>
<td>Maternal weight on day 7 of pregnancy, g</td>
<td>218.7 ± 2.67</td>
<td>237.9 ± 4.49</td>
<td>225 ± 3.70</td>
<td>211.3 ± 4.69</td>
<td>241.2 ± 3.68*</td>
</tr>
<tr>
<td>Maternal weight on day 14 of pregnancy, g</td>
<td>236.9 ± 2.42</td>
<td>248.2 ± 4.79</td>
<td>253 ± 5.82</td>
<td>228.1 ± 3.71</td>
<td>268.2 ± 4.44*</td>
</tr>
<tr>
<td>Maternal weight on day of birth, g</td>
<td>238.3 ± 2.80</td>
<td>229.7 ± 8.1</td>
<td>236.6 ± 5.92</td>
<td>231 ± 9.69</td>
<td>259.9 ± 4.62*</td>
</tr>
</tbody>
</table>

Values represent means ± SE. Pregnant dams were fed a high-fat (40% energy as fat) diet for either the first (HF1), second (HF2), or third (HF3) week, or all three (HF1–3) weeks of gestation. Control dams were maintained on a standard laboratory diet (10% fat). HF = high fat. Numerals refer to week(s) during gestation of maintenance on a high-fat diet. *P < 0.05 versus control; n = 6–8.
IN UTERO HIGH FAT DIET INDUCES ISLET CELL CHANGES

Table 2. Maternal circulating glucose and insulin concentrations

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HF1</th>
<th>HF2</th>
<th>HF3</th>
<th>HF1–3</th>
</tr>
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<tbody>
<tr>
<td>Blood glucose</td>
<td></td>
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<tr>
<td>concentrations</td>
<td>5.86±0.38</td>
<td>6.76±0.60</td>
<td>6.16±0.21</td>
<td>6.18±0.42</td>
<td>6.36±0.23</td>
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<tr>
<td>(mmol/l)</td>
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<td>before pregnancy</td>
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<tr>
<td>Blood glucose</td>
<td>6.61±0.41</td>
<td>6.86±0.42*</td>
<td>6.15±0.18</td>
<td>7.1±0.43</td>
<td>7.04±0.32*</td>
</tr>
<tr>
<td>concentrations</td>
<td></td>
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<tr>
<td>on day 7 of</td>
<td>5.51±0.29</td>
<td>5.07±0.19</td>
<td>5.81±0.15*</td>
<td>5.41±0.27</td>
<td>5.55±0.15*</td>
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<tr>
<td>pregnancy</td>
<td></td>
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<tr>
<td>Blood glucose</td>
<td>5.91±0.28</td>
<td>6.57±0.27</td>
<td>5.76±0.212</td>
<td>6.9±0.31*</td>
<td>6.74±0.21*</td>
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<tr>
<td>concentrations</td>
<td></td>
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<tr>
<td>on day of giving</td>
<td>126.6±25.34</td>
<td>74.56±20.26</td>
<td>135.9±68.01</td>
<td>67.15±9.06</td>
<td>176.5±82.16</td>
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<tr>
<td>birth, mmol/l</td>
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<tr>
<td>Serum insulin</td>
<td>173.7±78.96</td>
<td>137.5±36.5</td>
<td>55.05±15.89</td>
<td>152±40.84</td>
<td>217.7±32.58</td>
</tr>
<tr>
<td>concentrations</td>
<td></td>
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<tr>
<td>before pregnancy</td>
<td>166.4±60.83</td>
<td>91.84±21.25</td>
<td>229.1±57.69</td>
<td>97.13±17.42</td>
<td>215±29.89</td>
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<tr>
<td>(pM)</td>
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<tr>
<td>Serum insulin</td>
<td>152.1±40.82</td>
<td>178.8±54.41</td>
<td>81.78±23.1</td>
<td>169.7±42.2</td>
<td>155.9±25.62</td>
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<tr>
<td>concentrations</td>
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<td>on day of giving</td>
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<td>birth, pM</td>
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Values represent means ± SE. Pregnant dams were fed a high-fat (40% energy as fat) diet for either the first (HF1), second (HF2), or third (HF3) week, or all three (HF1–3) weeks of gestation. Control dams were maintained on a standard laboratory diet (10% fat). *P < 0.05 versus control; n = 6–8.

Neonatal birth weights. Significantly reduced birth weights were only found in HF1 neonates. Birth weights in the other experimental groups did not differ significantly from the control neonates (Fig. 1).

Neonatal circulating glucose and insulin concentrations. Blood glucose concentrations were significantly higher on day 7 of pregnancy in HF1 and HF1–3 dams (Table 2). HF2 and HF1–3 dams had significantly raised glycemia on gestational day 14. After giving birth, HF3 and HF1–3 dams were hyperglycemic. No significant differences in the serum insulin concentrations were evident between experimental dams, fed a HFD during gestation, and the control dams (Table 2).

Nutrition during the early phases of life is of major importance for proper tissue development and functional maturation (20). It has been suggested that exposure to an adverse environment in utero can program the physiology and metabolism of the offspring permanently, with long-term consequences for health in adulthood (35). During specific periods of gestation, we exposed rats to a maternal HFD to determine the effects of the diet on islet cell development.

The most profound changes in islet cell development were evident in neonates from dams exposed to a HFD throughout gestation, suggesting that increased duration of HFD exposure elicits a greater effect. Indeed, morphometric analysis of the islets showed that both the total volume and number of β-cells were significantly reduced in the hyperglycemic HF1–3 neonates. There are reports that hyperglycemia can decrease β-cell mass by inducing apoptosis (15, 43), and this could contribute...
to the reduced β-cell volume in HF1–3 neonates. In contrast, the α-cell volume, number, and size appear to be stimulated by a HFD in utero and were all significantly increased in HF1–3 neonates. Because these glucagon-secreting α-cells are functionally antagonistic to insulin, they could further stimulate glucose release into the circulation and therefore account for the hyperglycemia in HF1–3 neonates.

In rodent models of obesity without diabetes, there is an adaptive increase in β-cell mass to meet the insulin demands (18). Studies suggest that β-cell mass is also adaptively increased in non-diabetic obese humans (32). Beta-cell mass is regulated by the balance between β-cell replication and apoptosis and the development of new islets from pancreatic ducts by neogenesis (8, 17). Disruption of any of the pathways of β-cell formation or increased rates of β-cell death would result in decreased β-cell mass, and this would reduce capacity to produce insulin (38). Our data demonstrate compromised β-cell development in HF1–3 neonates. These results could be due to the HFD inhibiting β-cell replication pathways or inducing β-cell apoptosis. When adult mice were injected with streptozotocin to reduce β-cell numbers and induce hyperglycemia, exposure of islets to the high circulating glucose concentrations for an extended period resulted in gradual loss of their regenerative potential (24). It is possible, therefore, that the hyperglycemia evident in HF1–3 neonates may have inhibited islet neogenesis. Certainly, our results demonstrated that prolonged exposure of neonates to a HFD throughout pregnancy resulted in the most profound inhibition of β-cell development relative to those only exposed to a maternal HFD for a single week of gestation.

In HF1–3 neonates, the significantly reduced β-cell volume reflects the significant reduction in the number of β-cells. The effect of this reduction would be to increase the functional load for each individual β-cell, thereby making the maintenance of glucose homeostasis harder to achieve. It has been suggested that only a severe decrease in β-cell mass can cause diabetes because of the great reserve for insulin production of the endocrine pancreas (37). A reduced β-cell mass would however, subject β-cells to a persistently increased functional load, which, in the long term, may exhaust insulin release (37). We speculate that the compromised β-cell development and hyperglycemia, induced in HF1–3 neonates, could lead to β-cell failure later in life.

The pancreatic β-cell synthesizes, packages, and releases insulin on demand to maintain glucose homeostasis (14). In the study reported here, we found that HF1 and HF2 neonates were hypoglycemic. It is reported that the final week of gestation is the most quantitatively important phase of islet histogenesis (9). Interestingly, the HF3 neonates had both normal circulating glucose and insulin levels, suggesting a minimal effect of the HFD on these parameters at this stage.

Adult rats, fed a HFD (40% of energy as fat) for 4–21 wk, have been reported to have higher plasma glucose concentrations, fasting and postprandially, compared to rats fed a low-fat diet.
diet (5% energy as fat) (28). During pregnancy, circulating glucose concentrations of the dams were also significantly higher during the periods of their HFD feeding, suggesting that the HFD induces hyperglycemia in adult rats. Hyperglycemia, observed after delivery in HF3 and HF1–3 dams, was not, however, accompanied by hyperinsulinemia, which would have been a clear indication of gestational diabetes in these dams.

In addition to the altered circulating glucose levels, we have shown that dams fed a HFD during defined periods of gestation gave birth to offspring with altered islet cell architecture, wherein β-cell development was impaired and α-cell development was augmented. There were significantly fewer β-cells in HF1 neonates. The unaltered volume, number, and size of β- and α-cells in HF2 neonates indicated normal β- and α-cell development, suggesting that the second week of gestation is not a critical period of programming. Because the rat pancreas starts to develop during the second week of gestation and the endocrine pancreas in the final week of gestation, it is not surprising that the endocrine β- and α-cell development was not significantly influenced by the HFD insult during the middle week of gestation. However, HF3 neonates, exposed to a HFD for the final week of gestation when the endocrine pancreas develops, were found to have reduced β-cell number and larger α-cells. Indeed, the rapid increase in islet cell mass that occurs in late fetal and early neonatal life in the rat may explain why pancreatic morphology is so sensitive to nutritional insult during this specific period (44).

Our findings of larger α-cells in HF1, HF3, and HF1–3 neonates, as well as increased α-cell volume and number in the latter, suggested that an HFD has a stimulatory effect on α-cell development. It has been reported that the α-cell volume is significantly elevated, in weanling female mice, maintained on a high-protein diet, and both pancreatic and plasma glucagon concentrations are elevated (42). The increase in α-cell volume and pancreatic glucagon concentration initially appeared to be due to α-cell hypertrophy. The authors speculated that these changes were compensatory responses to the increased functional demand on α-cells (i.e., glucagon biosynthesis and secretion) imposed by chronic high-protein feeding (42). In our study, it appears that exposure to a maternal HFD throughout pregnancy has induced α-cell hypertrophy and hyperplasia, resulting in an increase in α-cell volume and number in the neonatal offspring. We therefore speculate that the stimulatory effect of the HFD in utero may modulate the expression of key genes involved in α-cell development, thereby resulting in accelerated α-cell number and size. This concept requires further investigation.

In our study, using an HFD instead of a low-protein diet, we have now found that dams fed a HFD for only the first week of gestation gave birth to pups (HF1 neonates) with significantly reduced birth weights, as was found in previous studies in rats fed an in utero protein-deficient diet (3, 34). Furthermore, women undernourished in the first trimester of pregnancy were found to produce small babies who developed hypertension as...
The feeding response, dams fed a HFD consumed more food, ingesting higher dietary fat and protein than dams maintained on a standard laboratory diet. However, the changes induced in the offspring, particularly in HFD–3 neonates, appear to be due to the high-fat content of the diet. In addition, the energy derived from carbohydrate was reduced in the HFD. By increasing the fat component of the diet, the levels of the other macronutrients would be affected. The protein derived from calories was kept similar in both the HFD and standard laboratory diet as protein deficiency has a deleterious effect on islet cell development (12). Therefore the carbohydrate levels were reduced in the HFD, which may be beneficial as high-carbohydrate feeding has been shown to cause the immediate onset of hyperinsulinemia in rats (1).

An HFD has been shown to be linked to the development of obesity, insulin resistance and type 2 diabetes (53). In contrast to earlier studies focusing on protein deficiency in utero, which were relevant in times of war and famine, this study focused on the impact of a HFD, which is more representative of the eating habits of the current society in both the developing and Westernized world. The data from this study are the first to show that HFD exposure in utero results in compromised β-cell development, altered glycemia and low birth weight in neonates. Our data support the concept of the programming of physiology and metabolism in offspring by manipulating maternal nutrition.

**Perspectives**

Exposure to a maternal HFD for only the first week of gestation resulted in hypoglycemic neonates with low birth weights. This may predispose them toward the development of type 2 diabetes later in life. Neonates exposed to an HFD for the entire duration of pregnancy were hyperglycemic with reduced β-cell volume and number. It appears that HFD exposure for only a single week of gestation does not greatly affect β- and α-cell development in the neonatal rat. However, in neonates that were exposed to a HFD throughout gestation, β-cell development is adversely affected, while, in contrast, α-cell development is augmented. It is important to monitor these changes after weaning and in adulthood to determine whether β-cell development recovers.

**ACKNOWLEDGMENTS**

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**REFERENCES**


