Programmed metabolic syndrome: prenatal undernutrition and postweaning overnutrition

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Desai M, Babu J, Ross MG. Programmed metabolic syndrome: prenatal undernutrition and postweaning overnutrition. Am J Physiol Regul Integr Comp Physiol 293: R2306–R2314, 2007. First published September 26, 2007; doi:10.1152/ajpregu.00783.2006.—Maternal nutrient restriction results in intrauterine growth restriction (IUGR) newborns that develop obesity despite normal postweaning diet. The epidemic of metabolic syndrome is attributed to programmed “thrifty phenotype” and exposure to Western diets. We hypothesized that programmed IUGR newborns would demonstrate greater susceptibility to obesity and metabolic abnormalities in response to high-fat diet. From day 10 to term gestation and lactation, control pregnant rats received ad libitum (AdLib) food, whereas study rats were 50% food restricted (FR). Cross-fostering techniques resulted in three offspring groups: control (AdLib/AdLib), FR during pregnancy (FR/AdLib), and FR during lactation (AdLib/FR). At 3 weeks, offspring were weaned to laboratory chow or high-fat calorie diet (9% vs. 17% calorie as fat). Body composition, appetite hormones, and glucose and lipid profiles were determined in 9-mo-old male and female offspring. High-fat diet had no effect on body weight of AdLib/AdLib, but significantly increased weights of FR/AdLib and AdLib/FR offspring. High-fat diet significantly increased body fat, reduced lean body mass, and accentuated plasma leptin but not ghrelin levels in both sexes in all groups. In males, high-fat diet caused a significant increase in glucose levels in all three groups with increased insulin levels in AdLib/AdLib and AdLib/FR, but not in FR/AdLib. In females, high-fat diet had no effect on glucose but significantly increased basal insulin among all three groups. High-fat diet caused hypertriglyceridemia in all three groups although only food-restricted females exhibited hypercholesterolemia. Sex and offspring phenotype-associated effects of high-fat diet indicate differing pathophysiologic mechanisms that require specific therapeutic approaches.

catch-up growth; obesity; appetite hormones; impaired glucose tolerance; lipid

IN THE UNITED STATES, THERE IS a current epidemic of metabolic syndrome (obesity, hypertension, diabetes). Sixty-five percent of United States adults are overweight, with 31% obese, and childhood obesity now accounts for 20% of the population (31). Similarly, the rates of hypertension and diabetes are markedly increasing in the adult U.S. population. Despite attempts at improving childhood nutrition and an industry of calorie restriction during the second half of rodent pregnancy results in growth-restricted offspring with reduced plasma leptin and increased ghrelin levels. After nursing by normally fed dams and subsequently provided with ad libitum standard laboratory chow, both male and female offspring develop classic metabolic syndrome with obesity, hypertension, and glucose intolerance, in association with elevated plasma leptin, insulin, and triglycerides (8, 9). In view of the contribution of human high-fat diets to the manifestation of programmed obesity, we hypothesized that programmed intrauterine growth restriction (IUGR) newborns would demonstrate an enhanced susceptibility to obesity and metabolic abnormalities in response to a high-fat diet. This would further allow delineation between diet-induced vs. developmentally programmed metabolic changes.

MATERIALS AND METHODS

Maternal rat diets. A model of IUGR in which rat dams that were 50% food restricted during pregnancy and lactation was used has been previously described (8). Studies were approved by the Animal Research Committee of Los Angeles Biomedical Research Institute at Harbor-University of California Los Angeles Medical Center and were in accordance with the American Association for Accreditation of Laboratory Care and National Institutes of Health guidelines. Briefly, first-time pregnant Sprague-Dawley rats (Charles River Laboratories, Hollister, CA) were housed in a facility with constant temperature and humidity and a controlled 12:12-h light-dark cycle. At 10 days of gestation, control rats (AdLib group; n = 12) were continued on an ad libitum diet of standard laboratory chow (LabDiet with changing work habits. In the late 1980s to 1990s, Barker and colleagues (1, 2, 14) provided epidemiologic evidence of the programming of offspring metabolic syndrome, demonstrating that low birth weight was a significant predictor of adult obesity, diabetes, and cardiovascular disease. Studies demonstrating the increased incidence of adult metabolic syndrome among low-birth-weight human infants have since been repeated, and the findings confirmed throughout the world (reviewed in Refs. 6, 12, and 29). Despite this convincing evidence of gestational programming, it remains uncertain why the association of low birth weight and adult obesity was not manifest or recognized until the 20th century. Notably, it is only during this era that humans have had nearly unlimited access to nutrient supply, akin to ad libitum food. Furthermore, only during the past several decades has the “Western high-fat” diet become commonplace.

Our previous studies demonstrated that 50% maternal nutrient restriction during the second half of rodent pregnancy results in growth-restricted offspring with reduced plasma leptin and increased ghrelin levels. After nursing by normally fed dams and subsequently provided with ad libitum standard laboratory chow, both male and female offspring develop classic metabolic syndrome with obesity, hypertension, and glucose intolerance, in association with elevated plasma leptin, insulin, and triglycerides (8, 9). In view of the contribution of human high-fat diets to the manifestation of programmed obesity, we hypothesized that programmed intrauterine growth restriction (IUGR) newborns would demonstrate an enhanced susceptibility to obesity and metabolic abnormalities in response to a high-fat diet. This would further allow delineation between diet-induced vs. developmentally programmed metabolic changes.
follows. After an overnight fast, D-glucose (1 mg/g body wt) was fasted overnight and underwent a glucose tolerance test (GTT) as (i.e., 6 males and 6 females from 6 litters and dietary regimen) were anesthetized using ketamine and xylazine (90 mg/kg and 10 mg/kg ip, respectively) and placed in a surgically made cage with warm-water bottles to avoid hypothermia. Rats subsequently underwent an invasive dual energy X-ray absorptiometry scanning, using the DXA system with software program for small animals (model QDR 4500A; Hologic, Bedford, MA). An in vivo scan of whole body composition was obtained, including lean and fat tissue mass, total mass, and percent body fat determination. Body composition. At 9 mo of age, six males and six females from six litters in each of three maternal feeding paradigms were weaned to normal laboratory chow (LabDiet 5001), and one male and one female were weaned to high-fat diet consisting of 330 g/kg LabDiet 5001, 330 g/kg full-fat sweetened condensed milk, 70 g/kg sucrose, and 270 g/kg water (7). This high-fat and high-calorie, Western-style diet was designed to be highly palatable and provided 17% of its energy content as protein, 67% as carbohydrate, and 16% as fat. In contrast, the laboratory chow provided 28% of its energy content as protein, 63% as carbohydrate, and only 9% as fat. Thus, there were three maternal feeding paradigms during pregnancy/lactation (AdLib or FR) and two offspring feeding paradigms (LabDiet or high-fat) examined for both male and females. The total number of offspring studied was six males and six females from six litters in each of three maternal feeding paradigms weaned to normal laboratory chow, and six males and six females from six litters in each of three maternal feeding paradigms weaned to high-fat diet. Offspring weight and food intake were monitored weekly until 9 mo of age.

Body composition. At 9 mo of age, six males and six females from six litters and dietary regimen were anesthetized using ketamine and xylazine (90 mg/kg and 10 mg/kg ip, respectively) and placed in a microisolator cage with warm-water bottles to avoid hypothermia. Rats subsequently underwent an invasive dual energy X-ray absorptiometry scanning, using the DXA system with software program for small animals (model QDR 4500A; Hologic, Bedford, MA). An in vivo scan of whole body composition was obtained, including lean and fat tissue mass, total mass, and percent body fat determination.

Glucone tolerance test. Following 48-h recovery, the same animals (i.e., 6 males and 6 females from 6 litters and dietary regimen) were fasted overnight and underwent a glucose tolerance test (GTT) as follows. After an overnight fast, t-glucose (1 mg/g body wt) was injected intraperitoneally in conscious rats. Blood for glucose measurement was taken by repeated needle sticks from tail vein at time 0 and 15, 30, 60, 120, and 180 min after glucose injection. During the bleed times, the rats were loosely restrained in the cloth towel. Plasma insulin levels (Rat Insulin RIA Kit; Linco Research, St. Charles, MO) were measured at time 0 and 180 min.

Blood/plasma parameters. Following 48-h recovery, the offspring were once again fasted overnight, and blood was collected via cardiac puncture in heparinized and EDTA/aprotinin (780 KIU/ml of blood) tubes. Blood glucose was determined using a B-Glucose Analyzer (HemoCue, Mission Viejo, CA). Plasma was analyzed for leptin (rat RIA kit (LINCO Research, MO)) and ghrelin (rat Ghrelin RIA kit; Phoenix Pharmaceuticals, Belmont, CA). Lipid levels were measured using reagents from Raichem (San Diego, CA) and were run on an automated Cobas-Mira chemistry analyzer (Roche Diagnostic Systems, Somerville, NJ). Plasma triglycerides (cat. no. 80008) and cholesterol (cat. no. 80015) concentrations were analyzed using Raichem enzymatic reagents with control serum level 2 (cat. no. 83082) and control serum level 2 (cat. no. 83083). The inter- and intra-assay variabilities were 4.9 and 3.0%, respectively, for triglycerides; 1.3 and 1.0%, respectively, for total cholesterol.

Statistical analysis. Body composition data, blood glucose, and plasma hormone and lipid measurements were analyzed using either two- or three-way ANOVA with Dunnett’s post hoc tests. Early maternal diet, offspring weaning diet, and sex were used as independent variables. Area under the curve (AUC) was computed for the GTT and repeated measures of ANOVA were used for GTT analysis. Since sex differences were evident, results are presented according to sex. Values are expressed as means ± SE.

RESULTS

Body composition. As previously reported (8), at 1 day after birth pups of food-restricted dams weighed significantly less than pups of ad libitum-fed dams consistent with IUGR (6.0 ± 0.3 vs. 7.1 ± 0.3 g, P < 0.01). At 3 wk of age (prior to high-fat or LabDiet), offspring that were exposed to maternal food restriction only during pregnancy (FR/AdLib) were significantly heavier (50 ± 1 vs. 45 ± 1 g, P < 0.01), whereas offspring exposed to maternal food restriction only during lactation (LabDiet/FR) were significantly smaller (28 ± 1 g) than control offspring (AdLib/AdLib).

Among males weaned to LabDiet, 9-mo-old AdLib/AdLib and AdLib/FR-lab offspring were of similar weight, although both groups weighed significantly less than FR/AdLib-lab offspring. When provided high-fat diet compared with normal LabDiet, FR/AdLib-high-fat and AdLib/FR-high-fat, although not AdLib/AdLib-high-fat, males gained increased weight. Body length was not affected by either of the maternal feeding paradigms or by offspring provided high-fat diet (Fig. 1). Body fat measurements demonstrated the previously reported marked increase in percentage body fat in FR/AdLib-LabDiet, although not AdLib/FR-LabDiet, compared with AdLib/AdLib-LabDiet (8). Offspring high-fat diet significantly increased percent body fat and reduced lean body mass in each of the three groups (Fig. 2). When expressed as ratio of body fat to body mass, the effect of high-fat diet on fat was greatest in FR/AdLib male offspring (high-fat: 0.43 ± 0.04 vs. LabDiet: 0.23 ± 0.02), followed by AdLib/FR (high-fat: 0.33 ± 0.03 vs. LabDiet: 0.19 ± 0.02) and AdLib/AdLib (high-fat: 0.26 ± 0.03 vs. LabDiet: 0.15 ± 0.01).

Among all comparative groups on both high-fat and LabDiet, females weighed significantly less than male offspring at 9 mo of age. Effects on body weight and composition were generally similar to that of males. As such, AdLib/AdLib-LabDiet and AdLib/FR-LabDiet females were of similar weight, although both groups weighed significantly less than FR/AdLib-LabDiet females. When provided high-fat diet, FR/AdLib-high-fat females gained increased weight and all three groups demonstrated increased body fat and reduced lean body mass (Figs. 1 and 2).

Food intake and appetite regulating hormones. Consistent with our previous findings (8), both males and females from FR/AdLib and AdLib/FR groups weaned to LabDiet consumed more food per gram body weight (Fig. 3). This was apparent from ages 4 to 8 wk, after which no differences were discernible among the groups. High-fat diet resulted in increased food intake among all groups, although sex differences were apparent. When expressed as kilocalories, offspring on high-fat diet consumed ~2,000 kcal/100 g more than those on Lab Diet. Once again, from ages 4 to 8 wk, food intake was increased in FR/AdLib and AdLib/FR males, whereas FR/AdLib and AdLib/FR females had comparable intake to AdLib/AdLib.

We further investigated plasma levels of hormones regulating appetite. Leptin, an appetite suppressant that is also associated with percent body fat, was correlated with food intake
Fig. 1. Body weight (top) and length (bottom) in 9-mo-old male and female offspring from AdLib/AdLib (control), FR/AdLib (FR in pregnancy), and AdLib/FR (FR in lactation) weaned to laboratory chow (black columns) or high-fat diet (white columns). AdLib, ad libitum food; FR, food-restricted. Values are means ± SE of n = 6 from 6 litters per group per diet for males and n = 6 from 6 litters per group per diet for females. *P < 0.01 vs. AdLib/AdLib and c; P < 0.01, laboratory chow vs. high-fat diet.

Fig. 2. Percentage body fat (top) and percentage lean body mass (bottom) in 9-mo-old male and female offspring from AdLib/AdLib (control), FR/AdLib (FR in pregnancy), and AdLib/FR (FR in lactation) weaned to laboratory chow (black columns) or high-fat diet (white columns). Values are means ± SE of n = 6 from 6 litters per group per sex. *P < 0.01 vs. AdLib/AdLib and c; P < 0.01, laboratory chow vs. high-fat diet.
and percent body fat among male offspring. Thus, FR/AdLib-LabDiet offspring demonstrated a significant increase in basal plasma leptin levels compared with AdLib/AdLib-LabDiet. As high-fat diet significantly increased percent body fat in all three groups, there was a parallel increase in basal plasma leptin levels. Plasma ghrelin, a hormone known to stimulate appetite, was significantly increased only in the AdLib/FR (both LabDiet and high-fat) group with notably no additional effect in response to the high-fat diet. Results for females were identical to that of males (Fig. 4).

**Plasma lipids.** Basal plasma triglyceride levels in the male offspring demonstrated a similar pattern as that of percent body fat and plasma leptin levels (Fig. 5). There was a significant increase in triglycerides in FR/AdLib-LabDiet offspring, and in response to high-fat diet, all three groups of offspring demonstrated an increase with levels highest among the FR/AdLib-high-fat males. There was no effect of any of the maternal feeding paradigms or postweaning diets on male plasma cholesterol levels.

Evidence of a sex effect was apparent in plasma lipids. Akin to the males from FR/AdLib-LabDiet group, the females also demonstrated a significant triglyceride increase. High-fat diet increased triglycerides to similar levels in all three female groups, unlike the exacerbation noted in the FR/AdLib-high-fat males. In contrast to the males, there was a significant increase in female cholesterol levels only among the FR/AdLib-high-fat and AdLib/FR-high-fat offspring.

Basal blood glucose and plasma insulin. (Fig. 6): As previously demonstrated FR/AdLib-LabDiet males exhibited a significant increase in basal blood glucose and insulin levels, whereas AdLib/FR-LabDiet males had glucose and insulin levels comparable to the AdLib/AdLib-LabDiet (9). High-fat diet resulted in a significant increase in basal blood glucose levels in all three groups. Notably, basal plasma insulin levels were increased in AdLib/AdLib-high-fat and AdLib/FR-high-fat male offspring, but not in the FR/AdLib-high-fat male offspring, which demonstrated elevated plasma insulin with LabDiet, resulting in all three groups having similar plasma insulin levels.

Once again, there were salient sex differences in basal blood glucose and plasma insulin responses. Analogous to males, FR/AdLib-LabDiet females had significantly increased blood glucose, whereas AdLib/FR-LabDiet females showed no change in glucose. However, unlike males, there was no independent affect of the high-fat diet on basal blood glucose in any of the three groups. Furthermore, the female FR/AdLib-LabDiet had significantly increased, whereas AdLib/FR-LabDiet had decreased basal insulin levels compared with AdLib/AdLib-LabDiet offspring. In contrast to males, high-fat diet induced a significant increase in basal plasma insulin among all three groups.

**GTT.** Male plasma insulin levels at 180 min following the glucose dose were increased in FR/AdLib-LabDiet, although not in AdLib/FR-LabDiet offspring. When the glucose AUC
Fig. 4. Plasma leptin (top) and ghrelin (bottom) levels in 9-mo-old male and female offspring from AdLib/AdLib (control), FR/AdLib (FR in pregnancy), and AdLib/FR (FR in lactation) weaned to laboratory chow (black columns) or high-fat diet (white columns). Values are means ± SE of n = 6 from 6 litters per group per diet per sex. *P < 0.001 vs. AdLib/AdLib and c; P < 0.01, laboratory chow vs. high-fat diet.

Fig. 5. Plasma triglycerides (top) and cholesterol (bottom) levels in 9-mo-old male and female offspring from AdLib/AdLib (control), FR/AdLib (FR in pregnancy), and AdLib/FR (FR in lactation) weaned to laboratory chow (black columns) or high-fat diet (white columns). Values are means ± SE of n = 6 from 6 litters per group per diet per sex. *P < 0.01 vs. control and c; P < 0.001, laboratory chow vs. high-fat diet.
Fig. 6. Basal blood glucose (top) and basal plasma insulin (bottom) levels in 9-mo-old male and female offspring from AdLib/AdLib (control), FR/AdLib (FR in pregnancy), and AdLib/FR (FR in lactation) weaned to laboratory chow (black columns) or high-fat diet (white columns). Values are means ± SE of n = 6 from 6 litters per group per diet per sex. *P < 0.01 vs. AdLib/AdLib and c; P < 0.01, laboratory chow vs. high-fat diet.

Fig. 7. Plasma insulin levels at 180 min following glucose dose (top) and area under the curve during GTT (bottom) in 9-mo-old male and female offspring from AdLib/AdLib (control), FR/AdLib (FR in pregnancy), and AdLib/FR (FR in lactation) weaned to laboratory chow (black columns) or high-fat diet (white columns). Values are means ± SE of n = 6 from 6 litters per group per diet per sex. *P < 0.01 vs. AdLib/AdLib and c; P < 0.01, laboratory chow vs. high-fat diet.
was examined over the 180 min. AdLib/AdLib-LabDiet offspring demonstrated the lowest blood glucose with intermediate values for the AdLib/FR-LabDiet and the highest values for the FR/AdLib-LabDiet offspring. High-fat diet resulted in an increase in plasma insulin levels at 180 min only in the AdLib/AdLib-high-fat and not in FR/AdLib-high-fat or AdLib/FR-high-fat male offspring, resulting in significantly increased AUC among FR/AdLib-high-fat and AdLib/FR-high-fat groups (Figs. 7 and 8).

Female plasma insulin levels at 180 min were also increased in FR/AdLib-LabDiet, although AdLib/FR-LabDiet females showed significantly decreased levels. Females demonstrated an increased glucose AUC in both FR/AdLib-LabDiet and AdLib/FR-LabDiet offspring. Unlike the males, the high-fat diet caused an increase in 180-min plasma insulin levels in all three groups, although only the AdLib/FR-high-fat group demonstrated an increase in the glucose AUC. Of note, the ranking was different from that of the males with the lowest values demonstrated by AdLib/AdLib-high-fat, intermediate values for the FR/AdLib-high-fat, and the highest levels for the AdLib/FR-high-fat offspring (Figs. 7 and 8).

**DISCUSSION**

We hypothesized that a postweaning Western high-fat diet would predispose IUGR newborns, more so than control newborns, to the development of adult obesity. Our results demonstrate that high-fat diet results in marked obesity in IUGR adult offspring (FR/AdLib), causing metabolic abnormalities that are sex specific and distinct from control-high-fat fed offspring (AdLib/AdLib).

In the present study, the high-fat diet resulted in a significant increase in body weight in FR/AdLib adult offspring, above that which occurs with LabDiet, although there was no difference in the body weight of control offspring fed Lab or high-fat diets. Among the both male and female FR/AdLib, the high-fat diet further increased percentage body fat and reduced percentage lean body mass. Despite the absence of a change in body weight in control offspring, the high-fat diet also resulted in increased percentage body fat, which was similar to that observed in the FR/AdLib group fed LabDiet. AdLib/FR offspring showed males demonstrating increased body fat and weight as did FR/AdLib offspring, whereas AdLib/FR females showed changes similar to control offspring. Previous studies have demonstrated the absence of an effect of the high-fat diet on body weight, suggesting that body weight alone is a poor indicator of adiposity (28, 35). The results of the present study indicate that the high-fat diet accentuates body fat accretion at the expense of lean body mass, particularly in FR/AdLib offspring and more so in the females. Importantly, these findings suggest a programmed alteration in metabolic pathways, which potentially serve to enhance adipogenesis. For instance, the regulation of adipocyte growth and function may be altered, causing increased adipocyte differentiation, adipocyte hypertrophy, and/or lipogenesis. Hence, the disproportionate increased percent

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**Fig. 8.** Glucose tolerance test (GTT) in 9-mo-old male and female offspring from AdLib/AdLib (control, ○), FR/AdLib (FR in pregnancy, ▽), and AdLib/FR (FR in lactation, ▼) weaned to laboratory chow (top) or high-fat diet (bottom). Values are means ± SE of n = 6 from 6 litters per group per diet per sex.
body fat vs. lean body mass in FR/AdLib offspring not only contributes to the obese phenotype but likely impacts glucose and lipid homeostasis as discussed below.

The high-fat-diet-related obesity may in part be attributed to enhanced appetite, and indeed all groups given high-fat diet had increased food intake compared with their counterparts fed regular LabDiet. Notably, male offspring from FR/AdLib and AdLib/FR fed the high-fat diet exhibit significantly increased food intake compared with the controls; and when the food intake was adjusted for body weight, hyperphagia was apparent from ages 4 to 8 wk, after which no differences were discernable among the groups. In contrast, female offspring from the three groups had similar food intake per gram body weight. Thus, high-fat-diet-mediated hyperphagia in FR/AdLib males may result from altered appetite regulation. We have previously demonstrated that these offspring are hyperleptinemic and have reduced anorexigenic response to peripheral leptin (10). In contrast, the absence of further hyperphagia in FR/AdLib-high-fat-fed females despite increased body weights, suggests an alternative mechanism for programmed obesity, which may include altered energy expenditure and/or efficient energy metabolism.

In offspring fed LabDiet, both male and female FR/AdLib evidence increased plasma triglyceride levels. The high-fat diet induced hypertriglyceridemia in both sexes from all three groups, although with a sex-specific effect response. Among males, high-fat diet significantly increased plasma triglycerides above the LabDiet values in all groups, causing marked hypertriglyceridemia in FR/AdLib males. In females, the high-fat diet increased plasma triglycerides to a similar extent, such that equivalent levels were seen in all three groups. Maternal diet (FR/AdLib, AdLib/FR) did not alter plasma cholesterol levels in either males or females fed LabDiet. Whereas there was no effect of high-fat diet on male plasma cholesterol in any group, the high-fat diet significantly increased female plasma cholesterol levels in FR/AdLib and AdLib/FR groups. The sex dimorphism in triglyceride and cholesterol levels may underlie enhanced adipose tissue lipolytic activity in males or, alternatively, impaired adipose tissue lipolytic activity in females (22, 26). This would signify increased lipid storage in adipose tissue vs. release in FR/AdLib females, and indeed this is reflected by greater increase in body fat. The sex-specific differences have been observed in humans (18, 24) as well as animal models (5, 33), and is thought to be mediated by estrogen as suggested by association between plasma lipoproteins and sex hormones (13, 21, 27, 30). Notably, our findings resemble the sexually dimorphic regulation of cholesterol homeostasis seen in the aromatase-knockout (ArKO) mouse, which is unable to synthesize endogenous estrogens. ArKO female mice develop hypercholesterolemia, whereas male ArKO mice exhibit elevated triglycerides (17, 20).

Among LabDiet-fed offspring, both male and female FR/AdLib rats exhibit basal hyperglycemia and hyperinsulinemia with an increased glucose AUC. A marked sex effect of high-fat diet was observed in glucose/insulin homeostasis. High-fat diet increased basal glucose in all groups of males but had no effect on any female group. Furthermore, high-fat diet increased plasma insulin in all groups except FR/AdLib males. When challenged with glucose, the deterioration in glucose homeostasis as evidenced by AUC was most evident in FR/AdLib males. Among most group the increased glucose, despite increased insulin, suggests a high-fat diet induced insulin resistance. Among FR/AdLib males the marked increase in glucose and the nonsignificant change in insulin suggest that maximum insulin secretory capacity had already been attained in response to LabDiet and that there is no further potential for increase with high-fat diet. The sex-specific findings in FR/AdLib-high-fat offspring are reminiscent of pancreatic islets of prediabetics where there is significantly more insulin secreted at each glucose concentration and of diabetics where there is impairment in the ability to respond to a glucose stimulus (11). Thus, FR/AdLib-high-fat males exhibit greater deterioration of glucose tolerance than females, a finding consistent with previous studies (15, 32).

Among AdLib/FR-high-fat male and females, basal plasma glucose and insulin were similar to that of controls-high-fat offspring whereas stimulated insulin response resembled that of FR/AdLib-high-fat offspring leading to increased GTT AUC. Specifically, the AdLib/FR-high-fat females demonstrated the highest levels of glucose AUC with modest increment in insulin levels. It is unclear whether this effect is a result of reduced pancreatic capacity for insulin secretion or alternatively to an increased plasma glucose threshold for insulin secretion among females. It would require additional degrees of insulin stimulation and/or measures of pancreatic insulin gene expression that differentiate set points from secretory capacity.

The primary mechanism linking fetal/postnatal growth with glucose impairment and dyslipidemia is not well understood, although factors influencing insulin sensitivity (9, 15, 32), alteration in the growth and microstructure of the liver (4, 5) and pancreas (3, 32), including alteration in the milk composition have all been implicated (16). In humans, the metabolic syndrome has been shown to be more prevalent in men than in women (1, 25). As rats represent an altricial species, the period of lactation has been correlated to the faster rate of growth in males (6, 29). Additionally, estrus assessment in the female developmental period and have attributed this phenomenon to the faster rate of growth in males (6, 29). Additionally, estrus assessment in the female offspring was not undertaken in the present study, it is likely that this may have impacted the magnitude of change noted in these parameters.

In summary, the findings of the present study signify three essential outcomes of postweaning high caloric, high-fat diet in the development of programmed metabolic syndrome. First, both maternal food-restricted and control offspring show similar although varying degree of response to food intake and appetite-regulating hormones. Second, food-restricted offspring show significant discernable effects on body composition and glucose/lipid profiles that are distinct from control-high-fat-fed offspring. Third, there is
sex-specific response to high-fat diet with males demonstrating adverse effect on glucose homeostasis and females on lipid profile. Thus, the specificity of response to high-fat diet provides a potential mechanism underlying altered metabolic regulation, which programs IUGR offspring to adult obesity. If extrapolated to the human condition, these studies have important implications for childhood and adult nutritional guidelines.

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REFERENCES


