Uteroplacental insufficiency alters hepatic fatty acid-metabolizing enzymes in juvenile and adult rats

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Lane, Robert H., David E. Kelley, Elisa M. Gruetzmaccher, and Sherin U. Devaskar. Uteroplacental insufficiency alters hepatic fatty acid-metabolizing enzymes in juvenile and adult rats. Am J Physiol Regulatory Integrative Comp Physiol 280: R183–R190, 2001.—Multiple adult morbidities are associated with intrauterine growth retardation (IUGR) including dyslipidemia. We hypothesized that uteroplacental insufficiency and subsequent IUGR in the rat would lead to altered hepatic fatty acid metabolism. To test this hypothesis, we quantified hepatic mRNA levels of acetyl-CoA carboxylase (ACC), carnitine palmitoyltransferase (CPTI), and the β-oxidation-trifunctional protein (HADH), fasting serum triglycerides, and hepatic malonyl-CoA levels at different ages in control and IUGR rats. Fetal gene expression of all three enzymes was decreased. Juvenile gene expression of CPTI and HADH continued to be decreased, whereas gene expression of ACC was increased. Serum triglycerides were unchanged. A sex-specific response was noted in the adult rats. In males, serum triglycerides, hepatic malonyl-CoA levels, and ACC mRNA levels were significantly increased, and CPTI and HADH mRNA levels were significantly decreased. In contrast, the female rats demonstrated no significant changes in these variables. These results suggest that uteroplacental insufficiency leads to altered hepatic fatty acid metabolism that may contribute to the adult dyslipidemia associated with low birth weight.

Uteroplacental insufficiency causes intrauterine growth retardation; syndrome X; dyslipidemia

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Furthermore, we determined whether changes in gene expression were associated with global dyslipidemia by quantifying fasting serum triglycerides on days 21 and 120 of life. We found that uteroplacental insufficiency resulted in long-term changes in gene expression of all three enzymes as well as decreased weight in the male IUGR rats. The fact that changes in gene expression secondary to in utero environmental perturbations occur long after the initial insult raises the possibility that our findings are secondary to epigenetic phenomena. Epigenetic changes in DNA are potentially inheritable, and both paternal and maternal birth weights in humans influence progeny size (18, 23, 24, 31, 36). Therefore, we additionally examined the influence of paternal versus maternal IUGR on the progeny weight.

METHODS

Animals. All procedures were approved by the Institutional Animal Care and Use Committee of the Magee-Womens Research Institute (Pittsburgh, PA). Timed pregnant Sprague-Dawley rats (Taconic Farms, Germantown, NY) were housed in individual cages and were exposed to 12:12-h light-dark cycles. All animals were fed routine Purina rat chow ad libitum (St. Louis, MO). The animals were allowed at least 2 days of acclimatization before experimental handling.

The rat model of uteroplacental insufficiency and IUGR used in this study is bilateral uterine artery ligation of the pregnant rat 48 h before term delivery. Fetal and neonatal rats in this model are significantly lighter than controls that undergo identical anesthesia and sham surgery, and litter size does not differ between control and IUGR groups (25). Like the human, the IUGR rat fetus is characterized by hypoxia, acidosis, altered insulin-like growth factor (IGF) availability, hypoglycemia, and hypoinsulinemia, all of which normalize in the perinatal period (40, 41, 59). At day 21 of gestation (term is 21.5 days), the maternal rats were anesthetized with intraperitoneal xylazine (8 mg/kg) and ketamine (40 mg/kg), and both inferior uterine arteries were ligated (IUGR; n = 24 litters). Sham surgery was performed on control animals that underwent identical anesthetic and surgical procedures except for the uterine artery ligation (Con; n = 24 litters) (26). Rats recovered within a few days after surgery and were weighed on day 3 of postnatal life.

Day 0 pups were delivered by cesarean section (n = 10 Con and IUGR, respectively). The remaining maternal rats were allowed to deliver spontaneously, and litters were randomly culled to six on day 3 of life (to control for the effects of litter size on growth). On day 21 of life, animals were separated from their dams for 4 h (to minimize individual hormonal variations associated with feeding) and sedated with isoflurane inhalation just before death (n = 8 Con and IUGR, respectively). On day 60 of life, animals were weighed. On day 120 of life, the remaining animals were fasted for 8 h and sedated with isoflurane just before death (n = 6 Con and IUGR, respectively). For both age groups, blood was drawn by cardiac puncture after sedation, and liver was immediately harvested and frozen.

Between days 45 and 75 of life, the following rat pairs were mated: Con male with Con female, Con male with IUGR female, IUGR male with Con female, and IUGR male with IUGR female (n = 3 for each pair). Rats used in these matings were randomly selected and not used for any further studies. Pups were allowed to deliver spontaneously and were weighed on day 7 of postnatal life.

RNA isolation. Total RNA was extracted from brain by the method of Chomczynski and Sacchi (9) and quantified in triplicate using ultraviolet absorbance at 260 nm. Gel electrophoresis confirmed the integrity of the samples. Bovine retinal RNA was prepared in a similar manner.

RT-PCR. A previously described and well-established method of semiquantitative RT-PCR was used for two reasons (28). First, RT-PCR requires relatively small amounts of tissues, which allowed quantification of multiple transcripts in fetal liver. Second, gene expression of all three enzymes correlate with enzyme activity (15, 44–46). CDNA was synthesized using random hexamers and Superscript II RT (Life Technologies, Gaithersburg, MD).

Amplification primers for ACC (30), CPTI (liver isoform (13), and HADHA (21) are listed in Table 1. For comparative purposes, RT-PCR was performed using primers for mitochondrial malate dehydrogenase (MMD) and isocitrate dehydrogenase (ICD), two Krebs cycle dehydrogenases not directly involved in fatty acid oxidation (Fig. 1) (17, 38). To determine reaction conditions when both amplicons were simultaneously produced exponentially, we reverse transcribed and amplified serial dilutions of rat RNA with standard amounts of retinal RNA under different conditions and cycle numbers. Once optimal conditions were determined, we ran a single-standard serial dilution with each quantification to regularly verify parallel production of both rat and bovine PCR-amplified products. Reactions were replicated three times once optimal PCR conditions were established, and the primer concentrations were identical across all ages and between study groups for each rat RNA target, respectively. The relative abundance of ACC, CPTI, and HADHA was quantified relative to that of a control rhodopsin band from the same reaction, which was assigned an arbitrary level of unity. To determine the specificity of the primers, the

Table 1. Sequences of PCR primers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sense Primer (5’-3’)</th>
<th>Antisense Primer (5’-3’)</th>
<th>Size of PCR Product</th>
<th>GenBank Accession No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>CACATCATGAGAGGAGGAGG</td>
<td>GTACATCACAGCGCTGGGTGC</td>
<td>276</td>
<td>J03808</td>
</tr>
<tr>
<td>CPTI</td>
<td>GCCATGCTGCGGATATGTG</td>
<td>GGCATGCCGGAATTGGCC</td>
<td>377</td>
<td>L07736</td>
</tr>
<tr>
<td>HADHA</td>
<td>TCAGCGCATAGCCATGCCTG</td>
<td>TGGAGTCACGGTTTCCACTCC</td>
<td>318</td>
<td>D16478</td>
</tr>
<tr>
<td>ICD</td>
<td>CAAGTCCTGCGGATGCGCTGG</td>
<td>CCGTCACAGCCTTTGTC</td>
<td>272</td>
<td>X71425</td>
</tr>
<tr>
<td>MMD</td>
<td>GTTCATGCTATGCTGGG</td>
<td>ATGCTCCTGCCTTCTTGAG</td>
<td>250</td>
<td>X04240</td>
</tr>
<tr>
<td>Rhodopsin</td>
<td>TATGCTCGACGCAGGAGG</td>
<td>ATGGGTAAAGATGTAGAAG</td>
<td>180</td>
<td>M21606</td>
</tr>
</tbody>
</table>

Sequences of each primer pair and their location in sequences cited in GenBank as noted. ACC, acetyl-CoA carboxylase; CPTI, carnitine palmitoyl transferase; HADHA, α-subunit of trifunctional protein of β-oxidation; ICD, isocitrate dehydrogenase; MMD, mitochondrial malate dehydrogenase.
amplified products were sequenced, and absolute identification was made.

**Hepatic malonyl-CoA Levels.** Malonyl-CoA was extracted from day 120 liver according to the method of Takeyama et al. (57). A reverse-phase high-performance liquid chromatography gradient procedure using a C18, 4-µm, 60A column with a C18, Nova-Pak guard column (Waters Nova-Pak, Watertown, MA) maintained at a 30°C temperature and the procedures of King and Reiss (22) were used for detection of malonyl-CoA. Concentrations of malonyl-CoA in the liver were calculated by comparing peak areas in the chromatograms with the respective peaks obtained using the malonyl-CoA standard; peak areas of serial dilutions of the standard (0, 18, 26, 72, and 144 pmol) were used to determine linear regression equations. The column was extensively washed between standards and samples to ensure no follow through of standard. The external standards were prepared with concentrations of malonyl-CoA determined by spectrophotometric absorption coefficients and then extracted as described [King and Reiss (22)]. Linearity of the peak areas for external standards was obtained (r = 0.95–0.99). Identification of peaks in liver samples was based on comparing time of elution with that of malonyl-CoA standards and by verifying that the malonyl-CoA peak was eliminated after alkalization of tissue extracts (hydrolyzing the acyl CoA ester) with subsequent augmentation of CoASH peak (and serving as a negative control).

**Serum triglycerides.** Serum triglycerides were measured on days 21 and 120 using a commercial kit from Sigma Diagnostics (St. Louis, MO). Reagents and samples were prepared according to the manual instructions, and absorbencies were measured in a spectrophotometer at 340 nm. Reliability of test results was monitored using sample blanks as well as use of control sera of known triglyceride concentrations (Sigma Cardiolipid Control).

**Statistics.** All data presented are expressed as means ± SE. For animal weights, hepatic malonyl-CoA levels, and serum triglycerides, statistical analyses were performed using ANOVA (Fisher’s protected least-significance difference) and Student’s unpaired t-test. For RT-PCR, statistical analyses were performed using the nonparametric Wilcoxon matched-pair test comparing the IUGR to its respective sham control group.

**RESULTS**

**Animals weights.** At day 60 of life (n = 6 litters), both male and female F1 IUGR rats were significantly lighter than Con rats (Table 2). At day 120 of life (n = 6 litters), IUGR male rats continued to weigh significantly less than their age-matched Con counterparts; however, in contrast, no significant difference in weight existed between day 120 IUGR and age-matched female Con rats (Table 2). Survival at day 120 did not differ between male and female rats at day 120 in either IUGR or Con groups.

Pups (F2 generation) of the paired matings were allowed to deliver spontaneously and were weighed on day 7 of life. There was no significant difference in parental weight within groups (e.g., IUGR males from 1 set of matings were similar in weight to that of the IUGR males from another set of matings) or litter size between pairings. Pups from matings that involved either an IUGR male or female (“heterozygous” for IUGR) weighed significantly less than progeny from Con-Con matings (Table 3). Pups from matings in which both parents were IUGR weighed significantly less than matings in which one parent was IUGR (Table 3).

**Hepatic mRNA levels.** We quantified relative mRNA levels of CPTI, HADHA, and ACC in IUGR and Con livers at days 0, 21, and 120 of life. At day 0 of life, table 2. Day 60 and day 120 male and fetal rate weights

| Table 2. Day 60 and day 120 male and fetal rate weights |
|---|---|---|---|
| Age | Male | Con | IUGR |
| 60 | 360 ± 10 | 307 ± 17* | 234 ± 3 |
| 120 | 626 ± 33 | 496 ± 29* | 320 ± 10 |

Values are means ± SE; n = 6 litters. *P < 0.05 intrauterine growth restricted (IUGR) vs. control (Con). Weight measured in grams.
In day 120 female rats, serum triglycerides were not significantly different between IUGR and Con animals (IUGR, 73 ± 13 mg/dl; Con, 64 ± 14 mg/dl; n = 6 both for Con and IUGR). However, serum triglycerides were increased approximately twofold in day 120 IUGR male rats versus Con (IUGR, 173 ± 30 mg/dl (P < 0.05); Con, 89 ± 11 mg/dl).

**DISCUSSION**

This present study finds changes in hepatic gene expression of key fatty acid-metabolizing enzymes CPTI, ACC, and HADHA mRNA in newborn, juvenile, and adult IUGR rats. The changes in adult male IUGR rats occur in association with increased hepatic malonyl-CoA levels and increased serum triglycerides, important markers of altered hepatic fatty acid metabolism. These novel observations are significant findings because they demonstrate a potential mechanism that links the altered in utero environment of uteroplacental insufficiency and subsequent adult dyslipidemia.

Like the human, the IUGR rat fetus is characterized by hypoxia, acidosis, altered IGF availability, hypoglycemia, and hypoinsulinemia, all of which normalize in the perinatal period (12, 39, 40, 59). Although little is reported about the effects of uteroplacental insufficiency on gene expression of hepatic fatty acid-metabolizing enzymes, our findings at day 0 of life of decreased hepatic mRNA levels of ACC, CPTI, and HADHA in the IUGR rat fetus correlate with identified mechanisms affecting their mRNA levels. For ACC, glucose and insulin levels directly regulate mRNA levels and enzyme activity so the hypoglycemia and hypoinsulinemia of the IUGR intrauterine milieu should lead to decreased hepatic ACC gene expression (16, 47). For CPTI and HADHA, coordinate mRNA levels of these genes are expected secondary to mutual dependence on Sp1 promoter binding for transcription as well as the altered redox state and oxidative stress experienced by the IUGR hepatocyte (43, 55). Oxidation of the transcription factor Sp1 decreases its DNA-binding efficiency and subsequently should decrease CPTI and HADHA transcription (1). As the hepatocyte redox state normalizes in the perinatal period, this effect should subside. The decreased expression of CPTI and HADHA, two enzymes involved in mitochondrial β-oxidation, is also consistent with the observation in the hypertriglyceridemia of the human IUGR neonate as a result of decreased peripheral fatty acid utilization (11, 50, 58). We speculate that decreased expression of CPTI and HADHA may provide an expla-

Table 3. Day 7 weights of Con and IUGR matings

<table>
<thead>
<tr>
<th>Mating</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con male- Con female</td>
<td>21.5 ± 1.2</td>
</tr>
<tr>
<td>Con male- IUGR female</td>
<td>14.4 ± 0.8*</td>
</tr>
<tr>
<td>IUGR male- Con female</td>
<td>13.8 ± 1.6*</td>
</tr>
<tr>
<td>IUGR male- IUGR female</td>
<td>10.3 ± 0.4*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 3 litters each pairing; *P < 0.05 vs. Con male- Con female; **P < 0.05 vs. Con male- IUGR female and IUGR male- Con female. Weights measured in grams.

hepatic mRNA levels of all three enzymes were significantly decreased in IUGR animals versus Con animals (Table 4 and Fig. 2A; n = 10 both for Con and IUGR). Similarly, at day 21 of life, mRNA levels of CPTI and HADHA continued to be significantly decreased, whereas mRNA levels of ACC doubled and were significantly increased (Table 4 and Fig. 2B; n = 8 both for Con and IUGR). At this age, no difference was noted between male and female animals.

At day 120 of life, our data were analyzed in a sex-specific context because of the relative difference in weights between IUGR male and female rats versus Con animals (n = 6 for each sex in each group). No significant difference was found between hepatic mRNA levels of CPTI, HADHA, and ACC in day 120 IUGR female livers versus age-matched Con female livers (Table 4) (Fig. 2C). However, hepatic mRNA levels of all three enzymes were significantly different between IUGR and Con males. Hepatic gene expression of CPT and HADH were significantly decreased, and hepatic gene expression of ACC was significantly increased in IUGR male rats (Table 4 and Fig. 2D).

mRNA levels of Con male and female rats at day 120 were also compared. For CPTI and HADHA mRNA, no significant difference existed between Con male and female adult rats. However, for ACC, male adult rats expressed 63 ± 5% (P < 0.05) of the mRNA levels that female adults rats expressed.

mRNA of ICD and MMD were also quantified for comparative reasons. No significance differences in mRNA levels of these enzymes were found between Con and IUGR or male and female rats at day 120 of life, respectively (Fig. 3).

**Hepatic malonyl-CoA levels.** We quantified hepatic malonyl-CoA levels in day 120 IUGR female and male rats. No differences were noted in hepatic malonyl-CoA levels between day 120 female IUGR and Con rats (Con female, 0.65 ± 0.05 nmol/g protein; IUGR female, 0.63 ± 0.07 nmol/g protein; n = 6 both for Con and IUGR). In contrast, hepatic malonyl-CoA levels were significantly elevated in day 120 IUGR male rats [Con male, 0.42 ± 0.07 nmol/g protein; IUGR male, 0.72 ± 0.08 nmol/g protein (P < 0.05); n = 6 both for Con and IUGR].

**Serum triglyceride levels.** We quantified fasting serum triglyceride levels in days 21 and 120 Con and IUGR rats. In day 21 rats, serum triglycerides were not significantly different between the sexes or the IUGR and Con rats (IUGR, 125 ± 24 mg/dl; Con, 90 ± 10 mg/dl; n = 8 both for Con and IUGR); hence, the results in males and females were pooled.

Table 4. mRNA levels of CPTI, HADHA, and ACC in Con and IUGR liver expressed as percentages of Con

<table>
<thead>
<tr>
<th></th>
<th>CPTI</th>
<th>HADHA</th>
<th>ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>54 ± 5%*</td>
<td>59 ± 9%*</td>
<td>57 ± 6%*</td>
</tr>
<tr>
<td>Day 21</td>
<td>29 ± 6%*</td>
<td>51 ± 7%*</td>
<td>201 ± 13%*</td>
</tr>
<tr>
<td>Female day 120</td>
<td>125 ± 18%*</td>
<td>90 ± 6%*</td>
<td>90 ± 12%*</td>
</tr>
<tr>
<td>Male day 120</td>
<td>34 ± 7%</td>
<td>30 ± 5%*</td>
<td>236 ± 19%*</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 IUGR vs. control.

This present study finds changes in hepatic gene expression of key fatty acid-metabolizing enzymes CPTI, ACC, and HADHA mRNA in newborn, juvenile, and adult IUGR rats. The changes in adult male IUGR rats occur in association with increased hepatic malonyl-CoA levels and increased serum triglycerides, important markers of altered hepatic fatty acid metabolism. These novel observations are significant findings because they demonstrate a potential mechanism that links the altered in utero environment of uteroplacental insufficiency and subsequent adult dyslipidemia.

Like the human, the IUGR rat fetus is characterized by hypoxia, acidosis, altered IGF availability, hypoglycemia, and hypoinsulinemia, all of which normalize in the perinatal period (12, 39, 40, 59). Although little is reported about the effects of uteroplacental insufficiency on gene expression of hepatic fatty acid-metabolizing enzymes, our findings at day 0 of life of decreased hepatic mRNA levels of ACC, CPTI, and HADHA in the IUGR rat fetus correlate with identified mechanisms affecting their mRNA levels. For ACC, glucose and insulin levels directly regulate mRNA levels and enzyme activity so the hypoglycemia and hypoinsulinemia of the IUGR intrauterine milieu should lead to decreased hepatic ACC gene expression (16, 47). For CPTI and HADHA, coordinate mRNA levels of these genes are expected secondary to mutual dependence on Sp1 promoter binding for transcription as well as the altered redox state and oxidative stress experienced by the IUGR hepatocyte (43, 55). Oxidation of the transcription factor Sp1 decreases its DNA-binding efficiency and subsequently should decrease CPTI and HADHA transcription (1). As the hepatocyte redox state normalizes in the perinatal period, this effect should subside. The decreased expression of CPTI and HADHA, two enzymes involved in mitochondrial β-oxidation, is also consistent with the observation in the hypertriglyceridemia of the human IUGR neonate as a result of decreased peripheral fatty acid utilization (11, 50, 58). We speculate that decreased expression of CPTI and HADHA may provide an expla-
nation for the relative hypertriglyceridemia often observed in IUGR newborns.

By adolescence, the lipid status of IUGR human individuals normalize (2). Similarly, perturbations induced by bilateral uterine artery ligation in the rat resolve and the IUGR rat undergoes a period of overt normalcy due to an apparent masking of metabolic changes. For example, prefasting and 24-h fasting levels of insulin, glucose, and glucagon levels are not significantly different between day 21 IUGR and Con animals (41). Similarly, we also found no significant difference in fasting serum triglycerides at day 21 of life, though gene expression of ACC, CPTI, and HADHA was still altered. The lack of correlation between a pattern of gene expression that suggests net hepatic fatty acid-triglyceride synthesis (increased ACC and decreased CPTI and HADHA) and serum triglycerides may be due to an altered pattern in hepatic fatty acid-metabolism regulation found specifically in the suckling-weaning transition when malonyl-CoA does not tightly regulate mitochondrial β-oxidation (10).

Malonyl-CoA does play a significant role in the regulation of hepatic mitochondrial fatty acid metabolism in hepatocytes from mature animals, and our findings of increased ACC and decreased CPTI and HADHA gene expression in the adult IUGR male rat parallels the increased hepatic malonyl-CoA levels and serum...
triglycerides, suggesting net hepatic fatty acid synthesis.

One other study has observed differences in adult fat metabolism between male and female rodents in response to in utero malnutrition. Lind et al. (29) found that induction of IUGR by maternal malnutrition caused hypercholesterolemia in the adult male guinea pig but not the female. Sexual dimorphism has also been noted in adult rat metabolism in response to an altered diet: male rats develop sucrose-induced plasma and hepatic hypertriglyceridemia, and female rats do not (19). Neither of these studies noted the effect of their intervention on hepatic gene expression.

It is also clear that human males and females process fat differently. The adult syndrome X quartet of hyperinsulinism, insulin resistance, hypertriglyceridemia, and hypertension is linked to low birth weight both in men and women; however, hepatic steatosis is more common in males than in females, and the positive relationship between insulin resistance and plasma triglycerides is weaker in women than in men (7, 32, 60). African-American men are more likely to demonstrate resistance to insulin-mediated suppression of adipocyte fatty acid release (56). These fatty acids are then available to the liver for synthesis into triglyceride-containing lipoproteins.

In contrast, adipocyte release of leptin correlates with total energy and resting energy expenditure in African-American women but not in men. The possibility that leptin may play a role in the gender differences associated with dyslipidemia and low birth weight is intriguing. The lowest levels of serum leptin concentrations are found in IUGR boys (6), and estrogen deficiency may trigger syndrome X in women (7, 8, 51, 53). We speculate estrogen deficiency would unmask differences in hepatic fatty acid gene expression and function in older sexually senescent IUGR female rats versus age-matched controls.

Our finding that progeny (F2 generation) of IUGR rats are also growth retarded regardless of which parental rat is IUGR supports the speculation that both male and female rats are affected, and moreover, suggests that the metabolic changes initiated by uteroplacental insufficiency alter gene expression by inheritable epigenetic phenomena, such as DNA methylation. Though promoter methylation patterns of the genes studied in this paper are unknown, it is likely that the epigenetic effects of uteroplacental insufficiency occur upstream in the cascade of events that regulate expression of ACC, CPTI, and HADH and allow for efficient fine tuning of multiple metabolic pathways. Our finding that low birth weight is inheritable through either parent mimics the human experience and demonstrates that nuclear genes are involved, although effects on the mitochondrial genome cannot be excluded (23, 24, 31). An epigenetic phenomena also potentially explains the observation in humans that less mortality occurs in growth-retarded infants whose mother was IUGR versus growth-retarded infants whose mother was not IUGR. The former group of infants may be growth retarded secondary to factors intrinsic to the fetus, whereas the latter group of infants is growth retarded secondary to an imposed pathological environment (49). The mechanisms by which the intrauterine milieu initiates epigenetic changes in fetal IUGR DNA should be the focus of future studies.

The association between fetal undernourishment and adult morbidities such as dyslipidemia is an important example of Barker’s “Fetal Origins of Adult Disease Hypothesis” (4). This hypothesis proposes that fetal adaptation to a deprived intrauterine milieu leads to permanent changes in cellular biology and whole body physiology. These adaptations ensure the survival of the immature animal under adverse conditions but may be detrimental to the adult. Altered hepatic fatty acid metabolism may be a result of either a primary metabolic imprint or a general metabolic imprint causing a secondary effect. Either way, this study makes a novel observation of an association between in utero malnutrition and adult hepatic gene expression and function of fatty acid-metabolizing enzymes.

Caution is necessary when attempting to apply data from a rat model to human pathophysiology. The timing and impact of uteroplacental insufficiency experienced by humans range across a continuum, and the human life experience is confounded by both genetic and environmental variables. In contrast, the laboratory rat in this study is inbred and experiences a homogeneous diet and environment. The insult imposed on the fetal rat in this model of uteroplacental insufficiency is severe, occurs relatively late in gestation, and results in asymmetrical growth retardation (brain growth is spared relative to carcass growth) (54). Similarly, most human IUGR infants are also categorized as asymmetrical. Characteristics of the asymmetric IUGR infant include a low ponderal index, and common etiologies include third trimester uteroplacental dysfunction or nutritional deficiency (14).

In summary, we found that uteroplacental insufficiency and subsequent low birth weight causes alterations in hepatic gene expression of ACC, CPTI, and HADHA in fetal, juvenile, and adult male rats. The changes in the adult male rat are associated with parallel changes in hepatic malonyl-CoA levels and serum triglycerides. We speculate that these changes may contribute to the adult dyslipidemia that is associated with low birth weight.

**Perspectives**

Our study focuses on the fetal origins of adult disease. We induce changes in fetal hepatic gene expression through uteroplacental insufficiency, a common human condition. The progression of the altered gene expression varies depending on the time of life and the sex of the animal, yet both sexes are affected based on the phenotype of the F2 progeny in our study. Future research will focus on which phenomena are primary effects of an altered intrauterine milieu and which are secondary effects. We speculate that the primary effect in this study is a “metabolic imprint” on the fetal DNA that initiates or selects a lifelong metabolic program.
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that endows the IUGR individual with a potential evolutionary advantage. A teleological explanation of our findings credits the fetus with interpreting the deprived intrauterine milieu as foreshadowing an adverse ex utero environment. If the IUGR fetus actively adapts to this prospective environment by programming the liver toward increased fatty acid synthesis or decreased fatty acid oxidation, then an increased supply of hepatic triglycerides may decrease skeletal muscle insulin sensitivity and spare glucose for the relatively large brain of the IUGR individual. Furthermore, transgenerational inheritance of growth retardation provides a selective group advantage by potentially allowing more bodies to fit into a limited environment. Recent advances in human life span and diet expose the morbidities associated with these and similar adaptations, particularly in western society, and thereby lead to a fetal origin of adult disease.

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