Anabolic effects of insulin and IGF-I in the ovine fetus are reduced by prolonged maternal fasting

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Shen, Weihua, Paul Wisniowski, Scott C. Denne, David W. Boyle, and Edward A. Liechty. Anabolic effects of insulin and IGF-I in the ovine fetus are reduced by prolonged maternal fasting. Am J Physiol Endocrinol Metab 288: E907–E913, 2005. First published January 11, 2005; doi:10.1152/ajpendo.00551.2004.—Fetal nutritional stress may result in intrauterine growth restriction and postnatal insulin resistance. To determine whether insulin resistance can begin in utero, we subjected late-gestation (130–135 days) ewes to 120 h of complete fasting and compared the results with our previous work in fed ewes (38). We determined the effect of insulin and/or recombinant human (rh)IGF-I infusion on ovine fetal phenylalanine kinetics, protein synthesis, and phenylalanine accretion. Experimental infusates were 1) saline, 2) rhIGF-I plus a replacement dose of insulin (40 nmol IGF-I/h + 16 μIU insulin/h), 3) insulin (890 μIU/h), and 4) IGF-I plus insulin (40 nmol IGF-I/h + 890 μIU insulin/h). During hormone infusion, both glucose and amino acid concentrations were clamped at basal concentrations. Amino acid infusion was required during infusion of either hormone to maintain plasma concentrations constant. However, the amount required during insulin infusion was less than during IGF-I infusion and 40% less than the amount required during identical studies in nonfasted animals. Phenylalanine used for protein synthesis and accretion was increased compared with control animals but again less so than in the nonfasted animals. In contrast to nonfasted animals, neither hormone increased the fractional synthetic rate of skeletal muscle protein nor that of plasma albumin. These results indicate that a short but severe nutritional stress can significantly alter the fetal anabolic response to insulin even when both glucose and amino acid substrate supplies are restored. Therefore, adaptive responses characterized by insulin resistance begin in utero when the fetus is subjected to sufficient nutritional stress.

protein synthesis; skeletal muscle; phenylalanine kinetics; fetal programming

INSULIN AND IGF-I are the major anabolic hormones in the fetus and neonate. However, in the case of either hormone, substrate supply is an important modulator of action. The major substrates for fetal growth and energy are glucose, glucose-derived lactate, and amino acids. These are all supplied in positive net quantities continuously to the fetus. Under normal circumstances, glucose is the major energy source, whereas amino acids provide substrate for both protein accretion and energy.

When the ewe undergoes prolonged fasting, the relative uptake and utilization pathways change significantly, as glucose supply declines by ≤50%; amino acid supply remains relatively constant, but their ratio of utilization for protein synthesis and oxidation changes dramatically in favor of oxidation (15, 16, 24). Previous studies have suggested that glucose supply is the major factor causing this change (21, 23), whereas the role of alterations in hormone sensitivity has remained unclear (22).

Epidemiological work in humans has suggested that prenatal nutritional state may induce life-long changes in hormone sensitivity, especially for insulin (1, 30, 31). This has been documented also in several animal models (8, 43). Adaptive changes in hormone sensitivity in utero are now hypothesized to predispose the organism to postnatal diseases, including obesity, type 2 diabetes, and the metabolic syndrome. A better understanding of the acute changes in fetal hormone action during fetal nutritional stress may improve our understanding as to how in utero nutritional stresses predispose the adult to insulin resistance.

The present study was designed to investigate the changes in anabolic hormone sensitivity that occur in the ovine fetus after a prolonged, 120-h total fast by the ewe. This represents 3.5% of the total gestation in the sheep and is equivalent to 6 days of fasting in a human gestation. Either rhIGF-I, insulin, or both were infused at pharmacological doses to determine maximal tissue sensitivity as measured by either substrate utilization or rates of protein synthesis. The study design was identical to that of our previous study in normally fed animals, thereby enabling us to determine the distinct effects of prolonged fasting (38). Although substrate was naturally limited during the fasting period, both glucose and amino acid concentrations were clamped during the metabolic studies, thereby eliminating acute substrate supply and/or alterations in plasma concentrations as a factor. Phenylalanine kinetics and accretion as well as glucose utilization were studied under control conditions and during infusion of pharmacological doses of insulin, IGF-I, or combined insulin plus IGF-I. We have previously documented that the anabolic effects of insulin are mediated by signal transduction via the phosphatidylinositol 3-kinase-mammalian target of rapamycin pathway, whereas IGF-I anabolic effects are independent of this pathway (37). The overall hypothesis of the study was that the insulin-signaling pathway would be most responsive to nutritional stress; therefore, we expected to see greater alterations in amino acid kinetics and accretion during insulin than during IGF-I infusion.

MATERIALS AND METHODS

Animals and surgical procedures. Twenty-three ewes of 115–120 days of gestation were utilized for this study. Animal care was in strict compliance with National Institutes of Health guidelines within an American Association for Laboratory Animal Care-certified facility.

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and the study protocols were approved by the Institutional Animal Care and Use Committee.

Surgical procedures were performed aseptically while the animals were under general anesthesia. Anesthesia was induced with intravenous ketamine and maintained with isoflurane inhalation. Fetal catheters were placed in the inferior vena cava, umbilical vein, and abdominal aorta; maternal catheters were placed in the inferior vena cava and abdominal aorta. Catheters were exteriorized and irrigated daily with 0.9% saline containing 50 U heparin/ml. All ewes consumed ad libitum a diet consisting of hay and pelleted alfalfa and had constant access to water and a salt lick.

Study design. The animals were allowed a minimum of 5 days of recovery from operative stress before the study. Complete recovery and fetal health were assessed by monitoring maternal food intake, fetal and maternal glucose concentrations, and acid-base status. Food was then removed and the ewe fasted for 5 days. Water and salt lick were provided continuously.

On the day of the study, baseline blood samples were obtained for amino acid, glucose, and hormone concentration assays. Then, the fetus was infused with one of the following four infusates: 1) saline, 2) recombinant human (rh)IGF-I (gift of Eli Lilly Research Laboratories, Indianapolis, IN) plus a replacement dose of insulin (40 nmol IGF-I/h + 16 mLU insulin/h), 3) insulin (890 mLU/h), and 4) IGF-I plus insulin (40 nmol IGF-I/h + 890 mLU insulin/h). The infusions were into the fetal inferior vena cava and continued for the duration of the 420-min study. The infusion rates of insulin and IGF-I were identical to those of our previous work, have been shown to result in pharmacological concentrations of insulin and IGF-I, and have been shown to affect amino acid and protein kinetics in the ovine fetus (4, 7, 18, 20). The dose of insulin infused in treatment 2 was expected to maintain plasma insulin concentrations at the baseline level, counteracting the inhibition of insulin secretion during the rhIGF-I infusion. In addition, L-[ring-2H5]phenylalanine (1.2 µmol/min), L-[2,6-3H]tyrosine (0.12 µmol/min), and L-[ring-2,6-2H]phenylalanine (0.66 µCi/min) were infused into the fetal inferior vena cava, and L-[1-13C]phenylalanine (3.6 µmol/min) was infused into the maternal inferior vena cava throughout the study.

During the hormone infusion, fetal whole blood glucose was clamped by frequent glucose concentration measurement with a glucose analyzer (YSI 2300; Yellow Springs Instrument, Yellow Spring, OH) and a variable infusion of 20% glucose. Likewise, the total fetal plasma branched-chain amino acid (BCAA) concentrations were measured at 15-min intervals (44), and a balanced amino acid solution (AminoSyn II; Abbott Laboratories, Abbott Park, IL) was infused at a variable rate to maintain plasma BCAA at the baseline level. Blood samples for analysis of metabolic substrates were obtained at 360, 380, 400, and 420 min. After the final blood samples were obtained, the ewe was anesthetized, and fetal size and fetal weight were recorded. All catheter placements were confirmed at autopsy.

Analytical methods. For the purpose of maintaining the amino acid clamp during the hormone infusion, total BCAA concentrations were monitored by spectrophotometry. However, for purposes of results reporting and kinetic calculations, the fetal plasma phenylalanine concentrations, tracer infused phenylalanine, and tyrosine concentrations were determined by standard ion exchange chromatography methodology utilizing a Beckman 6300 automated amino acid analyzer (Beckman-Coulter, Palo Alto, CA). Insulin concentrations in fetal plasma were determined in duplicate by a double-antibody radioimmunounassay (RIA) using ovine insulin to construct the standard curve (kit no. SRI-13K; Linco Research, St. Charles, MO). Total IGF-I in fetal plasma was determined by a validated competitive RIA that employed formic acid-acetone as the IGF-I extraction procedure (18).

Glucose was analyzed in whole blood by the glucose oxidase method (Boehringer Mannheim kit no. 189197). Intra-assay coefficient of variation was ±6%. The whole blood oxygen content was determined in duplicate with an automatic, direct reading by photometer (OSM-3; Radiometer, Copenhagen, Denmark). The within-animal coefficient of variation was 13% for arterial or venous oxygen contents. Phenylalanine and tyrosine isotopic enrichments were determined in plasma after derivatization to their tertiary butyldimethylsilyl (TBDMS) derivatives (36). These derivatives were injected into a Hewlett-Packard 5970 GC-MS (Hewlett-Packard, Palo Alto, CA) with electron impact ionization and selected ion monitoring of ions. Trazer-to-trace ratios were calculated by the method of Rosenblatt and Wolfe (32).

Phenylalanine and tyrosine kinetics, including phenylalanine conversion to tyrosine, were estimated by the method of Clark and Bier (5), modified for the fetus as we have previously described (17, 18). Phenylalanine kinetic parameters estimated by this model include rate of appearance (Raphen), phenylalanine irreversible disposal by hydroxylation, unidirectional flux of phenylalanine from maternal to fetal plasma (Fmmphen), phenylalanine used for protein synthesis (FSphen), and phenylalanine appearance from protein breakdown (PBphen). Muscle fractional protein synthetic rate was estimated by the ratio of specific activities of protein bound to plasma [13C]phenylalanine. Muscle tissue was obtained from fetal quadriceps at study completion immediately before euthanasia and snap-frozen in liquid nitrogen. Samples were homogenized and protein precipitated. The protein pellet was hydrolyzed, and radioactivity from phenylalanine was isolated by HPLC. Phenylalanine concentration in the hydrolysate was determined by AccQTag HPLC methodology (Waters, Milford, MA). Plasma phenylalanine concentration and tritium radioactivity were measured on a single sample after separation by HPLC. For determining plasma specific activity curves, additional blood samples were obtained at 10, 20, 40, 60, and 90 min after the beginning of the [13C]phenylalanine infusion. These data, in addition to the steady state, were fitted to a two-parameter exponential rise to maximum equation:

\[ f = a + (1 - e^{-k t}) \]

using SigmaPlot (SPSS, Chicago, IL). The area under the curve (AUC) of the resulting fitted equation was then determined. To determine the fractional synthetic rate, the specific activity of the skeletal muscle protein-bound fraction was divided by the plasma AUC. The results are expressed as µmol·day−1·kg−1.

Albumin fractional synthetic rate. Albumin was isolated by differential solubility in trichloroacetic acid-absolute alcohol (32, 50). The sample was dried by vacuum distillation and hydrolyzed by adding 1 ml of 4 N HCl into the dried albumin (40). Phenylalanine from albumin was enzymatically converted to phenylethylamine by L-tyrosine decarboxylase (9). TBDMS-phenylethylamine was formed, and the enrichment of TBDMS-[13C]phenylethylamine was determined by electron impact ionization and selected ion monitoring. The time-dependent slope of the albumin enrichment was determined using SigmaPlot. The fractional synthetic rate of albumin was calculated by dividing the increase (slope) in the enrichment of [13C]phenylalanine in albumin by the steady-state plasma [13C]phenylalanine enrichment over the same period (52).

Statistical analysis. The data were analyzed by two-way ANOVA, using insulin and IGF-I as independent factors (JMP; SAS, Cary, NC). All values are expressed as means ± SE. Main effects were taken to be significantly different if the F-test resulted in a P value of ≤0.05. Tukey’s honestly significant difference method was used for post hoc analysis of group differences. In the tables, the results of the post hoc analysis are given by symbols *, †, ‡, ‡‡, denoting group differences as detected by post hoc analysis; groups connected by the same symbol are not significantly different.

RESULTS

The fetal weights, maternal and fetal glucose concentrations, and fetal oxygen concentrations are given in Table 1. There were no significant differences in fetal weights among the four groups. Maternal glucose concentration was slightly higher in the control studies. There were also slight variations in the fetal
Table 1. *Fetal body weight and glucose and oxygen data*

<table>
<thead>
<tr>
<th></th>
<th>Weight, g</th>
<th>Maternal Glucose, mM</th>
<th>Fetal Glucose, mM</th>
<th>Fetal O2, mM</th>
<th>O2 Uptake, µmol·kg⁻¹·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4062 ± 266</td>
<td>1.96 ± 0.058*</td>
<td>0.486 ± 0.022†‡</td>
<td>0.835 ± 0.035</td>
<td>205 ± 40</td>
</tr>
<tr>
<td>IGF-I</td>
<td>3404 ± 326</td>
<td>1.72 ± 0.047†</td>
<td>0.617 ± 0.017*</td>
<td>0.739 ± 0.026</td>
<td>207 ± 23.3</td>
</tr>
<tr>
<td>Insulin</td>
<td>3599 ± 326</td>
<td>1.72 ± 0.064†</td>
<td>0.543 ± 0.022†</td>
<td>0.889 ± 0.038</td>
<td>226 ± 33</td>
</tr>
<tr>
<td>Both</td>
<td>3560 ± 302</td>
<td>1.68 ± 0.058†‡</td>
<td>0.426 ± 0.021†‡</td>
<td>0.783 ± 0.033</td>
<td>274 ± 34.4</td>
</tr>
</tbody>
</table>

Data are means ± SE. Means with different symbols *, †, ‡ are statistically different from one another (*P < 0.05).

Table 2. *Insulin, IGF-I, and IGF-II plasma concentrations during experimental infusions*

<table>
<thead>
<tr>
<th></th>
<th>Insulin, µU/ml</th>
<th>IGF-I, ng/ml</th>
<th>IGF-II, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.55 ± 4.67*</td>
<td>40.2 ± 20†‡</td>
<td>362 ± 33.8</td>
</tr>
<tr>
<td>IGF-I</td>
<td>2.05 ± 3.54*</td>
<td>316 ± 13.2†</td>
<td>414 ± 21.3</td>
</tr>
<tr>
<td>Insulin</td>
<td>38.5 ± 5.1††</td>
<td>38.8 ± 20.5*</td>
<td>419 ± 33</td>
</tr>
<tr>
<td>Both</td>
<td>73.8 ± 4.82†‡</td>
<td>292 ± 17.9†</td>
<td>432 ± 28.8†</td>
</tr>
</tbody>
</table>

Data are means ± SE. Means with different symbols *, † are statistically different from each other (*P < 0.05).
DISCUSSION

A major assumption of the “developmental origins of disease” paradigm is that the fetus responds to an adverse environment by downregulating growth, thereby sparing substrate and/or oxygen for vital life functions (9). The term “programming” is often used to indicate that essential fetal adaptations last beyond the fetal period, extending even into adulthood. Many of these adaptations involve alteration in metabolic response to anabolic hormones, especially insulin and IGF-I (41). Epidemiological studies have shown that insulin resistance, with its myriad complications, is a major risk to the organisms after experiencing intrauterine growth retardation (2, 30, 31). The present data demonstrate that resistance to the anabolic actions of insulin begins in utero when the fetus is sufficiently stressed.

We and others have documented that regulation of fetal growth results from a complex interaction between substrate supply and the resulting hormonal milieu (17, 19, 22, 38, 39). Our previous studies have demonstrated that glucose concentration was a significant factor determining amino acid catabolism and accretion (21, 23). However, amino acid availability was not controlled in those studies. The present study, in which amino acid concentrations were clamped by variable infusion of a balanced amino acid solution, extend our studies of the effect of insulin on rates of fetal amino acid accretion.

The major finding of interest in the present study is that, although hyperinsulinemia induces increases in protein synthesis and accretion above the basal rate, the magnitude of increase in accretion is less than in animals that have not been stressed by maternal fasting. Whole body rates of phenylalanine used for protein synthesis were $3.2 \pm 0.18$ µmol·kg$^{-1}$·min$^{-1}$, similar to fed animals studied under similar experimental protocols (38). However, protein synthesis in skeletal muscle was not
increased, in sharp contrast to the fed animals. In addition, phenylalanine accretion was only 0.69 ± 0.17 μmol·kg⁻¹·min⁻¹, 30% less than that found in the fed studies.

Data from previous studies have indicated that the decrease in the magnitude to which insulin stimulates amino acid accretion during maternal fasting may simply be due to decreased substrate availability (22). However, the present study precludes this conclusion, as both amino acids and glucose were supplied as needed to maintain plasma concentrations constant. Therefore, the rates of infusion for glucose and amino acids during the studies reflect the degree to which insulin or IGF-I stimulated utilization rates. We (38) have previously published an experiment with identical experimental protocol but in ewes that had not been fasted. Insulin and IGF-I concentrations were similar in the two studies; glucose concentrations were lower and leucine/phenylalanine concentrations higher in the present experiment, consistent with the fasted state. Figure 5 shows the rates of glucose and phenylalanine infusion in the present study compared with those of our previously published study. Insulin stimulated glucose utilization to a comparable degree in both studies. However, phenylalanine utilization during insulin infusion was markedly diminished; during fasting, only 40% as much amino acid solution was required as during the fed studies. This difference cannot be attributed to insulin concentrations, as pharmacological doses were used in both experiments, and the concentrations achieved during fasting were greater than during the fed studies.

A second major finding of the present study was a reversal in the anabolic potency of IGF-I relative to insulin. In the fed experiments, both phenylalanine utilization and accretion were stimulated by both hormones but to a greater extent by insulin (38). These data were similar to studies in neonatal piglets, where exquisite sensitivity to insulin is seen, especially after feeding (28). There was also a suggestion of a synergistic effect when the hormones were coinfused. During fasting, IGF-I stimulated phenylalanine utilization to a greater extent than insulin and with twice the effectiveness as during the fed experiments. It was equal with insulin in effecting phenylalanine accretion, whereas in the fed experiments it had been less effective.

We also measured the fractional protein synthesis rates in skeletal muscle. As with whole body synthesis, insulin stimulated fractional protein synthesis rates in skeletal muscle to a lesser extent relative to the fed experiments. In fact, in skeletal muscle, the fractional protein synthesis rate was statistically unchanged from control during any of the experimental conditions. In the fed experiments, the fractional protein synthesis rate was increased by 50–100% during hormone infusion. Likewise, the plasma albumin fractional protein synthesis rate was unchanged during infusion of either hormone, although there was a nonsignificant trend toward increased synthesis.

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This may be due to the comparatively large interanimal variance in albumin synthesis, with a resultant lack of power to detect changes. Therefore, at the of level either the whole body or the individual organ, anabolic insulin resistance is induced by severe fetal nutritional stress.

Controversy exists as to whether the associations between intrauterine growth retardation and insulin resistance are primarily the result of genetic background or intrauterine stress (9). This has resulted in two paradigms: the “thrifty genotype,” in which genetic makeup is paramount (27), and the “thrifty phenotype,” in which fetal adaptive responses to nutritional stress are paramount (10). It is likely that considerable overlap exists between these alternative hypotheses. Most existing studies either are epidemiological or have been performed in small mammals such as rats (11–14, 25, 40, 43) or mice (6), where genetic diversity may be limited. The present studies were performed in a large animal, the sheep, with considerably larger genetic diversity. Other investigators have also used the growth-retarded sheep to demonstrate alterations in placental substrate transport (33, 42) and pulmonary development (26). However, to our knowledge, this is the first demonstration of decreased anabolic action of insulin. It is also the first to show that such changes can occur in a relatively short period of time, given a sufficient stress. Therefore, our finding of decreased anabolic response to insulin in these studies supports the hypothesis that nutritional stress per se induces insulin resistance.

It is interesting that the insulin resistance occurs only in relation to amino acid and protein metabolism. Insulin-stimulated glucose utilization remained normal compared with unstimulated fetuses. This is important because glucose is the main oxidative fuel of the fetus (3). During fasting of the ewe, maternal and fetal glucose levels fall to very low levels (15, 16, 34, 35). Thus maintenance of normal glucose insulin sensitivity may be important for the fetus to be able to utilize the reduced but essential amounts of glucose yet available. On the other hand, by reducing the protein anabolic effects, amino acids are spared for use as an oxidative substrate.

In summary, the present study demonstrates that, during an acute severe nutritional stress, the ovine fetus adapts by decreasing the anabolic response to insulin even when amino acid substrates are supplied in adequate amounts. Glucose insulin sensitivity remains unchanged. The fetal anabolic response to IGF-1 also remains largely unchanged. The net result of these adaptations allows the fetus to maintain oxidative metabolism but at the expense of growth. These adaptations are consistent with the hypothesis that undernutrition programs the fetus to develop insulin resistance later in life, when substrate availability is sufficient.

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