0031-3998/88/2305-0480$02.00/0
PEDIATRIC RESEARCH

Vol. 23, No. 5, 1988
Printed in U.S.A.

Glucose Utilization by the Placenta and Fetal Tissues in Fed and Fasted Pregnant Rabbits

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ABSTRACT. Glucose utilization by the placenta and individual fetal tissues was studied *in vivo* in conscious pregnant rabbits at 29 days of gestation. In the fed state, the rate of glucose utilization was similar in the placenta and the gravid uterus, suggesting that the rate of fetal glucose utilization was approximately 40 nmol/min/g. A 96-h maternal fast induced a significant decrease in glucose utilization by the myoendometrium and in the glucose utilization index by fetal liver and brown adipose tissue. No modification was observed in other fetal tissues. These results indicate that glucose utilization by the placenta and the whole fetus from 96-h fasted rabbits does not decrease despite profound changes in endocrine and metabolic maternal parameters. (*Pediatr Res* 23: 480–483, 1988)

Abbreviations

FFA, free fatty acids
2DG, 2-deoxyl-[1-^{3}H]glucose
GU, glucose uptake
KB, ketone body

Metabolic requirements of the gravid uterus have been quantified *in vivo* in the cow (1) and the sheep (2) and more recently in the guinea pig (3) and the rabbit (4). The growth and oxidative metabolism of the mammalian fetus are largely dependent on the rates of fetal glucose and amino acid utilization (5). Most of these studies have been carried out using chronic vascular catheterization and measurements of overall substrate uptake by the fetus and the placenta by means of the Fick principle methodology. However, this technique does not permit determination of substrate utilization by individual tissues of the fetus in small mammalian species.

In this respect, the rabbit is of interest because: *1*) use of the radioactive 2-deoxyglucose technique, adapted to rodents (6) can be coupled to determination of blood flow and venous-arterial blood glucose concentration difference across the uterus; *2*) maternal FFA cross the placenta in this species (7) and can potentially replace glucose as fuel for fetal tissues, particularly during maternal fasting when increased amounts of FFA are transferred to the fetus (8). The aim herein was to quantify glucose utilization by individual tissues in the fetal rabbit and to determine the partition of glucose between the myoendometrium, the placenta, and the fetus in the fed and fasted state. The experiments were performed on day 29 of gestation in chronically catheterized pregnant rabbits.

Received July 13, 1987; accepted January 6, 1988.
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MATERIALS AND METHODS

Animals. Female rabbits from the "Fauve de Bourgogne" strain were obtained from a commercial breeder and were housed in individual stainless steel cages. Mating was performed in the laboratory and the day of mating was taken as day zero of pregnancy. On day 25 of gestation pregnant rabbits were separated into two groups. The first group was fed a solid commercial rabbit diet *ad libitum* (caloric percentage:carbohydrate 68%, protein 22%, fat 10%) (Sanders Laboratory, Paris, France) until day 29 of gestation; food intake was measured daily. The second group was fasted for 96 h. All animals had free access to water.

Surgical procedure. Surgery was carried out on day 21 of pregnancy under ketamine hydrochloride (35 mg/kg intramuscularly) and xylazine hydrochloride (6 mg/kg intramuscularly) anesthesia. Under sterile conditions maternal vessels were catheterized. Polyvinyl catheters were inserted into one jugular vein to allow radioactive tracer infusions and into one femoral artery and one branch of the uterine vein for blood sampling under conscious, unrestrained conditions (4). In addition, an intracardiac catheter was advanced to the left ventricle through the right carotid artery to allow blood flow measurements (4). All catheters were tied in place and tunneled subcutaneously to exit into a plastic cap sutured into place in the interscapular region. Catheters were filled with an heparinized solution (800 IU/ml saline) and were flushed every 3 days to keep them patent. Detailed description of the surgical procedures has been reported previously (4).

Measurements of glucose utilization by the placenta, the uterus, and fetal tissues. Experiments were carried out *in vivo* on day 29 of gestation in fed and 96-h fasted does. The radioactive 2-deoxyglucose technique recently adapted to the rat fetus was used (9, 10). Glucose utilization index was determined in individual tissues after an intravenous injection of 250 μCi 2DG in the conscious pregnant rabbits. Maternal arterial blood was sampled at 1, 3, 5, 10, 15, 20, 40, 60, 80, and 120 min after the radioactive 2DG injection for the determination of radioactive 2DG and of glucose concentrations.

The ^{3}H-2DG-6-phosphate which accumulates in various tissues cannot be further metabolized and represents an index of glucose used inasmuch as any molecule of glucose which enters the cell is phosphorylated before being incorporated into glycogen or metabolized through the glycolytic pathway. The accumulation of ^{3}H-2DG-6-phosphate in various tissues was measured in steady state conditions for blood glucose concentration and glucose utilization rates as described in the adult rat (6).

Tissue and blood sampling. Maternal arterial blood was withdrawn from the femoral artery just before and 120 min after the 2DG injection. At 120 min, after maternal laparotomy, fetal blood was obtained from axillary vessels under pentobarbital anesthesia (11). During fetal blood sampling, the placenta was left *in situ* and the maternal glycemia remained constant, indicating that fetal biochemical parameters are representative of the maternal steady state. At the end of the experiments, mothers

were killed by an overdose of pentobarbital and two fetoplacental units adjacent to the ovaries were rapidly excised and the portion of the uterine horn surrounding one fetus and its placenta was carefully dissected out. The myoendometrium, placenta, and fetus corresponding to each fetoplacental unit were removed and weighed. Uterine, placenta, and individual fetal tissues (hindlimb muscle, diaphragm, heart, liver, brain, skin, and white and brown adipose tissue) were rapidly dissected out. These tissues have very low glucose-6-phosphatase activity at this stage of gestation (12, 13) and thus the hydrolysis of 2DG-6-phosphate back to 2DG was considered to be negligible. Determinations of radioactivity in blood samples and measurements of tissue ^{3}H-2DG-6-phosphate content were performed according to the technique described previously in the rat (6, 10).

Determination of the lumped constant for the gravid uterus. The lumped constant that is a correction factor for the discrimination against 2-deoxyglucose in glucose transport and phosphorylation pathways was determined *in vivo* for one fetoplacental unit (fetus, placenta, and surrounding myoendometrium). It is represented by the difference between maternal and fetal blood radioactive 2DG/glucose specific activity because axillary blood of the fetus represents efferent blood from the uteroplacenta (9). A primed continuous venous infusion of 2-deoxy-[1-^{14}C]glucose (0.52 μCi/min) in saline was performed during 60 min to obtain a steady blood 2DG specific activity. Blood samples were then obtained in steady state conditions (9) through the maternal femoral artery and via axillary fetal vessels. The samples were deproteinized and the supernatants were treated as described previously (6). The ratio of maternal arterial blood ^{14}C-2DG/glucose to fetal blood ^{14}C-2DG/glucose was found to be 0.81 ± 0.04 (n = 7) and was not significantly altered by fasting: 0.72 ± 0.04 (n = 6).

Calculation of glucose utilization index by various tissues. The glucose utilization index was expressed as ^{3}H-2DG-6-phosphate content of each fetal tissue divided by the integral of the ratio of maternal arterial blood ^{3}H-2DG to glucose over a 120-min period. In the present experiments, the lumped constant of fetal tissues was not determined and the results were expressed as glucose utilization indices rather than glucose utilization rates. For the placenta and myoendometrium, the rates of glucose utilization were calculated by dividing the glucose utilization index by the calculated lumped constant.

Measurement of total glucose uterine uptake. The GU by one fetoplacental unit was measured using the Fick principle methodology and calculated according to the formula: GU (nmol/min/g) = venous-arterial glucose concentration difference across the uterus (μmol/ml) × uteroplacental blood flow (ml/min/g). Both variables were measured in steady state conditions in fed and fasted pregnant rabbits. Paired venous and arterial blood samples were drawn simultaneously as described previously (4). Uteroplacental blood flow was measured in conscious animals using radioactive microspheres labeled with ^{113}Tin (NEN, Dreleich, W. Germany). Calculations of uterine blood flows were done by the reference sample method (4).

Biochemical measurements. Blood glucose concentration was determined by the glucose oxidase method (Boehringer, Meylan, France) on blood supernatant deproteinized with $Ba(OH)_2$-$ZnSO_4$. Blood ketone body and lactate concentrations were measured on neutralized perchloric acid (6%, w/v) supernatants (14, 15). Plasma FFA concentrations were measured by an enzymatic method (NEFA C kit, Biolyon, Lyon, France) (4). Plasma insulin was determined by radioimmunoassay on aliquots of the last blood samples using rabbit insulin as standard (16).

Statistics. Results are presented as means ± SEM. Statistical differences were evaluated using the Student's t test.

RESULTS

Metabolic and hormonal changes induced by maternal fasting. Maternal, fetal, uteroplacental weights, and blood flow remained unchanged after a maternal fast of 96 h (Table 1). Changes in fetal and maternal endocrine and metabolic parameters are shown in Table 2. Maternal fasting for 96 h was associated with a 20% decrease in blood glucose, a 5-fold increase in blood KB concentration and a 2-fold increase in plasma FFA concentration. By contrast, the changes induced by fasting were smaller in the fetuses than in the mothers. Although blood glucose was decreased and ketonemia raised, the differences observed did not reach statistical significance. Fetal plasma FFA concentration was increased 3-fold ($p < 0.01$). The permeability of the rabbit placenta to glucose, FFA, and KB was estimated by calculating maternofetal substrate concentration gradients (Fig. 1). Whereas maternofetal gradients for glucose and FFA were not significantly lowered during maternal fasting, an important decrease of maternofetal KB gradient was observed, suggesting a limited transfer of KB from maternal to fetal circulation. Both fetal and maternal plasma insulin concentrations were markedly decreased by maternal fasting (Table 2).

Glucose utilization by the fetoplacental unit. The rates of glucose utilization by the placenta, the myoendometrium, and the fetoplacental unit (myoendometrium + placenta + fetus) are shown in Figure 2. Results are expressed as rates of glucose utilization inasmuch as values obtained for the myoendome-

Table 1. *Fetoplacental parameters in 29-day pregnant rabbits (mean ± SE)*

	Maternal wt (g)	Mean fetal wt (g)	Mean placental wt (g)	Mean wt of one fetoplacental unit (g)	Mean placental blood flow (ml/min)	Mean uteroplacental blood flow (ml/min)
Fed (n = 7)	3800 ± 200	39 ± 3	6.3 ± 0.7	58 ± 1	3.28 ± 0.18	4.45 ± 0.32
96-h fasted (n = 7)	3600 ± 100	34 ± 3	5.8 ± 0.7	57 ± 4	3.07 ± 0.39	4.20 ± 0.43

Table 2. *Blood substrates (mmol/liter) and plasma insulin (μU/ml) concentrations in 29-day fed or fasted pregnant rabbits and their fetuses (mean ± SE)*

	Glucose	3-Hydroxybutyrate	Acetoacetate	Lactate	FFA	Insulin
Mothers						
Fed (n = 7)	5.43 ± 0.17	0.21 ± 0.05	0.17 ± 0.06	1.40 ± 0.09	0.79 ± 0.17	48 ± 8
96-h fasted (n = 7)	4.44 ± 0.22*	1.2 ± 0.4*	0.87 ± 0.10*	1.65 ± 0.27 (NS)	1.62 ± 0.20†	2 ± 1*
Fetuses						
Fed (n = 11)	4.21 ± 0.22	0.16 ± 0.08	0.19 ± 0.06	8.0 ± 1.0	0.06 ± 0.01	115 ± 19
96-h fasted (n = 12)	3.66 ± 0.17 (NS)	0.35 ± 0.18 (NS)	0.30 ± 0.07 (NS)	6.5 ± 1.1 (NS)	0.19 ± 0.04†	21 ± 4*

p values refer to differences between fasted and fed state. * $p < 0.001$, † $p < 0.01$.

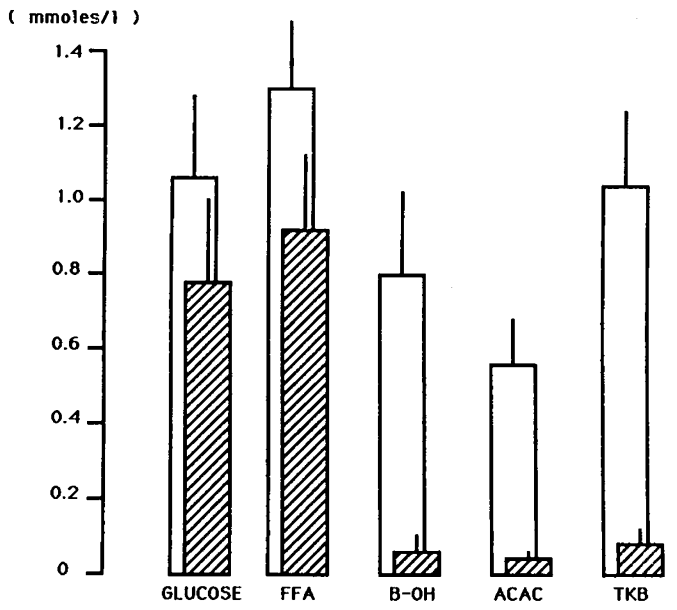

Fig. 1. Maternofetal substrate concentration gradients in fed □ and fasted ▨ pregnant rabbits. *B-OH*, 3 hydroxybutyrate; *AcAc*, acetoacetate; TKB, total KB.

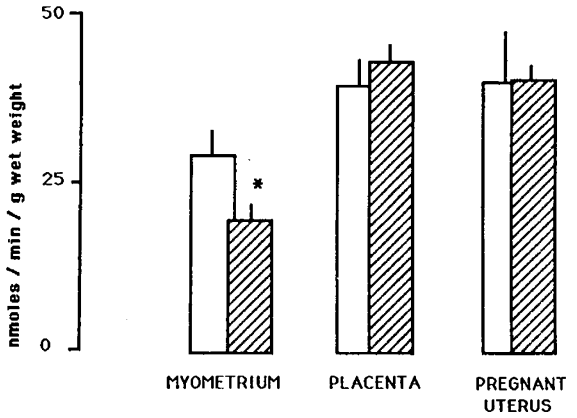

Fig. 2. Glucose utilization in myometrium (uterine muscle), placenta, and one fetoplacental unit (fetus + placenta + myometrium) in fed □ and 96-h fasted ▨ pregnant rabbits. * $p < 0.01$.

trium and the placenta have been corrected by the mean lumped constant (0.76) of the gravid uterus (see "Materials and methods"). In the fed state, placental glucose utilization measured by the radioactive 2DG method (40.5 ± 3.9 nmol/min/g) is in the range of values obtained by the Fick method for the fetoplacental unit (41.1 ± 7.2 nmol/min/g). Glucose utilization by the myoendometrium (29.9 ± 3.9 nmol/min/g) was not statistically different ($p > 0.05$) from placental glucose utilization (40.5 ± 3.9 nmol/min/g). After maternal fasting, glucose utilization was significantly decreased (−33%) in the myoendometrium ($p < 0.01$) but remained unchanged in the placenta and the fetoplacental unit.

Glucose utilization index in individual fetal tissues. The glucose utilization index of liver and brown adipose tissue (Fig. 3) were significantly decreased in fetuses from fasted mothers (11 ± 0.5 *versus* 7.2 ± 0.5 and 27 ± 2.2 *versus* 7.8 ± 1.2 nmol/min/g, respectively). By contrast, the glucose utilization index of fetal muscles (hindlimb, diaphragm, heart), white adipose tissue, skin, and brain was not modified by maternal fasting.

DISCUSSION

The fetoplacental unit is a complex structure composed of the fetus and the placenta attached to the surrounding myoendometrium. In a number of mammalian species the gravid uterus is composed of only one fetus and one placenta, and therefore quantitative information concerning a single fetoplacental unit in politocus species such as the rabbit is useful for interspecies comparisons. The results obtained *in vivo* under physiological conditions indicate that in the rabbit the rate of glucose utilization by the placenta is similar to the rate of glucose utilization by the fetoplacental unit. This suggests that fetal glucose utilization is in the same range as the placental glucose utilization because fetal mass represents 80 to 90% of the total fetoplacental unit mass (Fig. 2; Table 1). This study also demonstrates that glucose utilization measured simultaneously in the same animal using two different techniques (radioactive 2-deoxyglucose and Fick principle methodology) gives very similar values. Interspecies comparison indicates that, near the term, the epitheliochorial placenta of the sheep (2) utilizes three to five times more glucose than the hemochorial placenta of man (17), rat (18), and rabbit (Fig. 2).

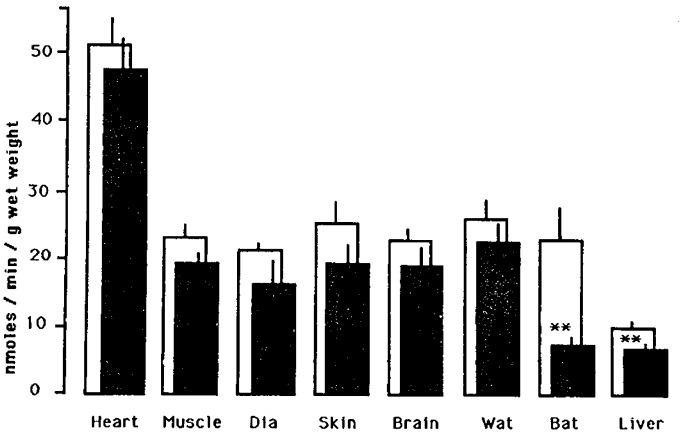

Fig. 3. Glucose utilization index of individual tissues in fetuses from fed □ and 96-h fasted ■ mothers. *Dia*, diaphragm; *Wat*, perirenal white adipose tissue; *Bat*, interscapular brown adipose tissue.

A 96-h maternal fast beginning on day 25 of gestation does not decrease glucose utilization rates in the placenta and the fetoplacental unit (Fig. 2). The absence of effects of maternal fasting on placental blood flow and glucose utilization by the fetoplacental unit seems to be specific for the rabbit because large decreases in placental blood flow and glucose utilization have been observed in rat and sheep (18–21). Fetal metabolic response to maternal fasting can be analyzed on the basis of the changes occurring in blood substrate and plasma hormone concentrations in mothers and fetuses (Table 2). The significant decrease in maternal blood glucose was not reflected to the same extent in the fetus, suggesting two hypotheses: *1*) an increased placental transport capacity to maintain adequate glucose transfer from maternal to fetal circulation; and/or *2*) a rapid adaptation of fetal metabolism (increased liver glycogenolysis and gluconeogenesis) to compensate for a decrease in placental transfer of glucose. The present data do not permit determination of which mechanism is operative, but a premature appearance of fetal liver gluconeogenesis has been shown to occur during maternal fasting in the rabbit (22, 23). The fall in fetal plasma insulin observed during maternal fasting could be explained by the fact that the fetal pancreas is sensitive to small changes of fetal glucose concentration as demonstrated *in vitro* (24) and *in vivo* (25) in the rat and in the sheep (26, 27). The decrease in fetal plasma insulin during fasting could be subsequently responsible for the premature induction of fetal liver phosphoenolpyruvate carboxykinase, the rate limiting enzyme of gluconeogenesis (22, 23), and thereby preserve fetal glucose homeostasis.

Another point to stress is the selective transfer of fat-derived substrates across the rabbit placenta. Despite very high KB concentration in maternal plasma, KB were not transported to a large extent from maternal to fetal circulation during

maternal fasting (Table 2; Fig. 2). Thus, in the rabbit, as in the sheep (28), KB cannot serve as alternative fuels for fetal tissues. This is in contrast to what occurs in the rat where a large amount of KB is transferred to the fetus during maternal fasting (29–31). By contrast, a significant transplacental transfer of FFA occurs during maternal fasting in the rabbit as evidenced by the 3-fold increase in fetal plasma (Table 2; Fig. 1). Whether or not FFA was used as an energy source in the fetal rabbit was not determined herein but it has been shown that FFA can be stored as triglycerides in liver and adipose tissue (8, 32, 33).

Use of the glucose analog, 2DG, permits measurement of glucose utilization by individual fetal tissues in animal species where small size does not allow vascular catheterization in the fetus. In addition, this technique may help to determine whether specific modifications occur in individual fetal tissues during maternal fasting, which may be masked when estimating the overall glucose utilization rate by the fetoplacental unit. *In vivo*, in the fed state, glucose utilization indices are similar in most fetal tissues studied (hindlimb muscles, diaphragm, white and brown adipose tissue, skin, and brain), *i.e.* about 25 nmol/min/g tissue, but differ in the heart (55 nmol/min/g) and the liver (11 nmol/min/g). *In utero* the heart exhibits the highest rate of glucose utilization among fetal tissues similar to the ventricle in the adult rat (34) and rabbit (35). It is noteworthy that in the fetal rabbit, basal and fasted glucose metabolic indices are 5 to 10 times lower than those measured in the fetal rat (10). These data further emphasize the species specificity previously pointed out for placental blood flow and glucose utilization rate. The maintenance of a constant glucose utilization index in most fetal tissues after 96 h of maternal fasting is probably due to the fact that fetal blood glucose concentration was not significantly decreased. In addition, these results suggest that most fetal tissues are not affected by hypoinsulinemia when blood glucose concentration remains constant. This is in contrast to data obtained *in vivo* in the fetal lamb (36) where fetal glucose uptake is correlated with arterial plasma insulin levels and in the fetal rat (10) where the rate of glucose utilization in several fetal tissues is increased by exogenous insulin. During maternal fasting in the rabbit, brown adipose tissue and liver are the only fetal tissues in which glucose utilization indices are significantly decreased. Both tissues possess insulin receptors that can be phosphorylated as early as day 20 of gestation (37). Thus the decreased glucose utilization observed in these tissues in the presence of fetal hypoinsulinemia in the fetuses of fasted mothers could be interpreted as a sign of a higher insulin sensitivity in comparison to other fetal tissues.

In conclusion, this study has demonstrated that the rabbit fetus maintains a physiological blood glucose level and normal rates of glucose utilization in most tissues after a 96-h maternal fast during late gestation. This suggests that selective and specific adaptations may be set up within the fetoplacental unit to protect the fetus and the placenta from the adverse effects of maternal undernutrition.

Acknowledgments. The authors are indebted to R. and J. P. Urbe and G. Orain for taking care of the animals and M. Fernandez for the preparation of the manuscript.

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