Chronic Maternal Hypoxia Retards Fetal Growth and Increases Glucose Utilization of Select Fetal Tissues in the Rat

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The development of intrauterine growth retardation (IUGR) is frequently associated with fetal hypoxia, hypoglycemia, and abnormal fetal glucose metabolism. To determine the effects of hypoxia (without concomitant hypoglycemia) on fetal glucose metabolism, we continuously exposed pregnant rats to 10% (10.1 kPa) ambient oxygen from day 15 through day 20 of gestation (term, 21.5 days) and used radiolabeled 2-deoxyglucose (2DG) to measure in vivo relative glucose utilization (rGU) of several fetal tissues on day 20 of gestation. Pair-fed rats in room-air oxygen were used as controls. Maternal hypoxia resulted in significant IUGR, fetal hypoxia and acidosis, and fetal lactate accumulation on day 20 of gestation. Following 5 days of hypoxia, rGU values for fetal lung, heart, and kidney were increased by 61%, 54%, and 47%, respectively ($P < .05$). rGU values for fetal brain, liver, muscle, and placenta were not significantly affected. Fetal plasma glucose concentrations were similar in hypoxic and control fetuses. We speculate that the increased rGU of hypoxic fetal tissues is due in part to anaerobic metabolism and increased glycolysis.

FETAL GROWTH is dependent on adequate availability of metabolic fuels and oxygen. Although multiple etiologies of intrauterine growth retardation (IUGR) exist, many are associated with limited nutrient and oxygen delivery to the fetus. A frequently used rodent model of IUGR is maternal uterine artery ligation, a procedure that limits glucose and oxygen availability to the fetus by reducing uterine blood flow.[1-4] Using this model, we have shown that relative glucose utilization (rGU) by fetal liver, heart, muscle, and kidney is increased 48 hours following ligation.[5] The increased rGU occurred despite decreased fetal plasma glucose and insulin concentrations.

Subsequently, we studied the effects of acute and chronic insulin-induced maternal hypoglycemia on fetal tissue rGU.[6] This model produces fetal hypoglycemia to a magnitude similar to that resulting from uterine artery ligation, but does not alter fetal blood gases or pH.[7] As expected, the resultant fetal growth retardation was not as severe as with uterine artery ligation. Maternal hypoglycemia of either 2 or 5 days' duration decreased the rGU of fetal liver, lung, muscle, and kidney. rGU of fetal heart was decreased after 2 days, but was normal after 5 days of hypoglycemia.

Since the two aforementioned models differ with respect to oxygen delivery to the fetus, we hypothesized that fetal hypoxia causes a change from aerobic to anaerobic metabolism, thus resulting in a greater demand for glucose following uterine artery ligation. In this study, we exposed pregnant rats to 10% (10.1 kPa) ambient oxygen during the third trimester of pregnancy in an effort to produce fetal hypoxia without altering fetal glucose concentrations. We then examined the effects of fetal hypoxia on fetal tissue rGU, fetal growth, and lactic acid accumulation.

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MATERIALS AND METHODS

Female Sprague-Dawley rats weighing 175 to 199 g were purchased from Harlan Laboratories (Madison, WI). Females in estrus were housed overnight with males, and mating was confirmed by the presence of spermatozoa in the vaginal smear the following morning (day 0). On day 14 of gestation (term, 21.5 days), each pregnant rat was anesthetized with intraperitoneal injections of xylazine 8 mg/kg and ketamine 40 mg/kg, and the left jugular vein and carotid artery were catheterized with sterile polyvinyl tubing. Rats were allowed to recover for 24 hours, at which time hypoxia-exposed rats were placed in a sealed, plastic chamber. The oxygen concentration in the chamber was incrementally reduced to 10% (10.1 kPa) over the next 24 hours using a mixture of compressed air and nitrogen. Oxygen and CO_2 concentrations in the chamber were monitored daily (Instrumentation Laboratory O_2 Monitor, Lexington, MA, and Ohmeda 5200 CO_2 Monitor, Englewood, CO). Carbon dioxide levels were maintained at less than 0.1% (0.1 kPa) by adjusting gas flow. Hypoxia-exposed rats had free access to standard food and water, and daily food intake was recorded. Control rats were mated 1 to 2 days after hypoxia-exposed rats and were housed in open cages. They were fed an amount of food equivalent to that consumed by the hypoxia-exposed rats from day 15 through day 20 of gestation. Maternal arterial blood gases (ABL 300, Radiometer, Copenhagen, Denmark) and plasma glucose concentrations (Beckman Glucose Analyzer II, Fullerton, CA) were obtained periodically from day 15 onward. During blood sampling and rGU measurements, hypoxia-exposed rats were quickly removed from the chamber and placed in a restraint within a smaller hypoxic chamber to allow access to the catheters while maintaining a fraction of inspired O_2 (FIO_2) of 0.1.

Fetal rat tissue rGU was determined on day 20 of gestation after 5 days of hypoxia using a modification of Sokoloff's 2-deoxyglucose (2DG) method.[5,8-10] A description of the methodology and its validation have been discussed previously.[5,6] In brief, nine hypoxic and nine control rats were injected with 370 kBq (10 μCi) 2-[^{3}H(G)]-deoxy-D-glucose (New England Nuclear, Boston, MA; specific activity, 263 kBq/nmol) via the jugular catheter. Maternal arterial blood was obtained at 1, 3, 5, 10, 15, 25, 35, and 43 minutes after injection. After obtaining the final blood sample, the rat received pentobarbital 40 mg/kg intravenously. At 45 minutes, four fetuses from the midportion of the uterine horns were removed, weighed, decapitated, and frozen in liquid nitrogen. Approximately 100-mg portions of the placenta (villous chorion), liver, and lung, and the entire heart, brain, kidney, and hindlimb muscles were removed from each frozen fetus and weighed. Fetal tissue

rGU was calculated using the equation

$$rGU = \frac{[2DG6P]\ T\ (\text{fetal tissue})}{P_k \int_0^T \frac{[2DG]\ t}{[\text{glucose}]}\ dt\ (\text{maternal plasma})},$$

where [2DG6P] is the fetal tissue activity of [^{3}H]2-deoxyglucose-6-phosphate at 45 minutes, [2DG]/[glucose] is the maternal plasma specific activity of [^{3}H]2DG, and P_k is the ratio between fetal and maternal plasma specific activities of [^{3}H]2DG. Fetal tissue [^{3}H]2DG6P activity and maternal plasma [^{3}H]2DG specific activity were determined as previously described.[5] The integral of the maternal [^{3}H]2DG specific activity was obtained by establishing the best-fitting curve using the double-exponential equation $y = Ae^{Bx} + Ce^{Dx} + E$, where A, B, C, D, and E are constants chosen by a curve-fitting program (In Plot, Graph Pad, San Diego, CA). This equation provides a measure of rGU, since differences may exist between 2DG and glucose with respect to cellular transport and phosphorylation.

P_k values were determined using an additional nine hypoxic and eight control rats. These values must be known, since changes in maternal glucose metabolism or uterine blood flow may potentially alter tracer and glucose provision to the fetus. Each rat was anesthetized with pentobarbital 40 mg/kg intravenously, and after a tracheostomy, each was ventilated with a small-animal ventilator. Hypoxia-exposed rats were ventilated in a F_{IO_2} of 0.1 at 90 breaths per minute with a tidal volume of 1.7 mL, and control rats were ventilated in a F_{IO_2} of 0.21 at 80 breaths per minute with a tidal volume of 1.7 mL. These parameters were chosen because they result in similar maternal blood gas values as in nonanesthetized rats. After stabilization an abdominal incision was made, exposing the uterine horns. [^{3}H]2DG was injected into the maternal jugular catheter, and maternal arterial blood was collected at the same time intervals as before. Fetal blood samples were obtained by severing the right axillary artery with the placental circulation intact.[11] Fetal blood was obtained at 2, 4, 6, 11, 16, 21, 26, 31, 36, and 44 minutes after 2DG injection by sequential sampling of multiple fetuses in each litter (Fig 3).

Fetal blood gases and lactate concentrations were determined from a separate group of six control and six hypoxia-exposed rats treated with the same experimental protocol. On day 20 of gestation, maternal rats were anesthetized and ventilated as described earlier. Blood was collected from multiple fetuses per litter, again by severing the right axillary artery with the placental circulation intact. Fetal blood was obtained 5 to 10 minutes after initiation of anesthesia and ventilation.

Maternal and fetal plasma insulin concentrations were determined using a double-antibody radioimmunoassay. Whole-blood lactate was determined using a spectrophotometric kit (Sigma no. 826-UV, St Louis, MO). This protocol was approved by the Institutional Animal Care and Use Committee of Evanston Hospital.

Data were analyzed with unpaired, two-tailed *t* tests. Data of unequal variance were analyzed with Mann-Whitney two-sample tests. Data obtained from multiple fetuses in a single litter were averaged. Each litter represented a single experiment. The results are presented as the mean ± SEM.

RESULTS

Maternal and Fetal Blood Gas Values

Exposure to 10% oxygen resulted in significant maternal hypoxemia and a compensated metabolic acidosis (Fig 1). A 43% to 53% reduction in maternal Pa_{O_2} was observed from days 16 through 20. Hypoxia-exposed rats developed a metabolic acidosis that was totally compensated by hyperventilation, except on day 19 when a slight but significant decrease in pH was observed.

Maternal hypoxia also produced significant fetal hypoxia and acidosis on day 20 of gestation (Table 1). Although fetal Pa_{CO_2} was lower in hypoxic fetuses, this did not completely correct the marked metabolic acidosis, and consequently fetal pH was reduced.

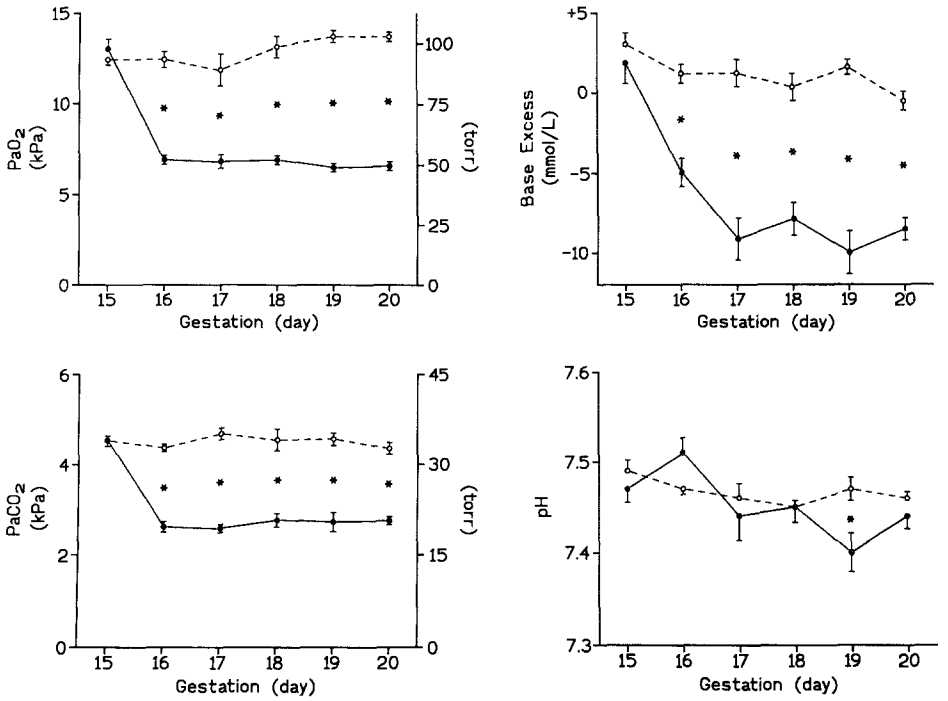

Fig 1. Arterial blood gas values in hypoxic (—) and control (----) maternal rats. *$P < .05$, hypoxia *v* control. n ≥ 5 for all data points.

Table 1. Fetal Blood Gas Values on Day 20 of Gestation

	Pao_2		$Paco_2$			
	kPa	mm Hg	kPa	mm Hg	pH	Base Excess (mmol/L)
Hypoxia	1.8 ± 0.1*	14 ± 0.7*	7.0 ± 0.4†	52 ± 3†	7.10 ± 0.03*	−13.8 ± 1.0*
Control	3.1 ± 0.1	23 ± 1.1	8.4 ± 0.4	63 ± 3	7.26 ± 0.02	−0.7 ± 1.0

*$P < .01$, hypoxia *v* control.
†$P < .05$, hypoxia *v* control.

Plasma Glucose and Insulin Concentrations

Hypoxia-exposed maternal rats had significantly elevated plasma glucose concentrations on days 17 and 18 (Fig 2). Slightly higher glucose levels were observed on days 16 and 19, but these did not reach statistical significance. Although day-20 glucose concentrations were nearly identical, hypoxic mothers had significant elevations in plasma insulin on that day (59.6 ± 9.1 *v* 34.5 ± 4.9 μU/mL, $P < .05$). Hypoxic and control fetal plasma glucose concentrations were not statistically different on day 20 (3.47 ± 0.21 *v* 3.62 ± 0.11 mmol/L, $P = .16$). Insulin concentrations were also elevated in hypoxic fetuses (233 ± 20 *v* 171 ± 12 μU/mL, $P < .05$). Fetal to maternal glucose ratios were not significantly affected by hypoxia (0.62 ± 0.04 *v* 0.68 ± 0.02, $P = .16$).

Maternal Food Intake and Weight Gain, and Fetal Body and Tissue Weight

Total food intake (days 15 to 20) for hypoxia-exposed rats was not statistically different than for control rats (62.0 ± 3.1 *v* 58.0 ± 3.5 g, $P = .41$). However, hypoxic rats demonstrated poor weight gain over the 5 days (3.7 ± 2.9 *v* 25.3 ± 2.8 g, $P < .001$). Litter size was not affected by hypoxia (11.6 ± 0.5 *v* 11.5 ± 0.5, $P = .94$). Exposure to 10% oxygen was associated with significant fetal growth retardation (3.22 ± 0.10 *v* 3.51 ± 0.09 g, $P < .05$). Liver, lung, kidney, and carcass (body after removal of head and viscera) were significantly lighter in hypoxic fetuses, whereas the weights of fetal brain, heart, and placenta were not significantly affected (Table 2).

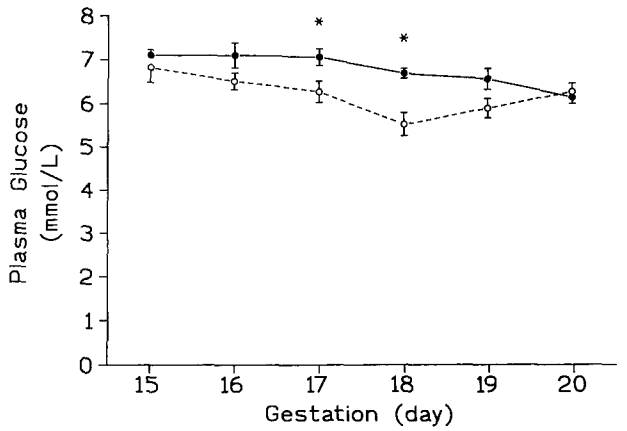

Fig 2. Plasma glucose concentrations in hypoxic (—) and control (---) maternal rats. Hypoxia was initiated after day-15 blood sample. *$P < .05$, hypoxia *v* control. n ≥ 6 for all data points.

P_k

Figure 3 depicts a typical course of [^{3}H]2DG specific activity in maternal and fetal plasma during a sample P_k determination. P_k values were not significantly different in hypoxic and control rats (1.15 ± 0.04 *v* 1.13 ± 0.02, $P = .66$).

rGU

Maternal exposure to 10% oxygen resulted in increased rGU of fetal lung, heart, and kidney (Fig 4). rGU values for fetal brain, liver, muscle, and placenta were not statistically different after 5 days of hypoxia.

Lactic Acid Concentrations

Hypoxia resulted in elevated blood lactate concentrations in both the mother (6.15 ± 1.4 *v* 2.44 ± 0.29 mmol/L, $P < .01$) and the fetus (12.73 ± 1.68 *v* 7.78 ± 0.63, $P < .05$).

DISCUSSION

IUGR is often associated with fetal hypoxia. To determine the effects of hypoxia on fetal glucose metabolism, we exposed pregnant rats to 10% oxygen during the third trimester and measured fetal tissue rGU near term. This technique produces fetal hypoxia and acidosis and increases the rGU of several fetal tissues. Although other glucose metabolites were not measured, the increase in fetal blood lactate concentrations during hypoxia suggests a greater rate of anaerobic metabolism and may explain the observed increased rGU of fetal lung, heart, and kidney.

The rate at which glucose is used is regulated by several different processes, including: (1) glucose availability; (2) activity, type, and quantity of glucose transporters and hexokinases; (3) tissue glucose requirements; and (4) humoral factors, eg, insulin, insulin-like growth factors, and catecholamines. Perturbations in any of these processes may alter glucose transport and/or phosphorylation, the two regulatory steps of glucose utilization.

Maternal hypoxia does not appear to disrupt fetal glucose availability, since fetal glucose concentrations and maternal to fetal glucose ratios remain normal. Although it is possible that fetal hypoxia directly affects glucose transport and phosphorylation, it is more likely that hypoxia alters tissue glucose utilization by increasing the demand or requirements for glucose. The elevated fetal blood lactate concentrations during hypoxia indicate an increase in anaerobic metabolism. The amount of adenosine triphosphate generated during anaerobic metabolism is substantially less than that produced during aerobic metabolism. Therefore, glucose requirements and glucose utilization are likely to increase during hypoxia.

Table 2. Fetal Tissue Weight on Day 20 of Gestation

	Brain (mg)	Liver (mg)	Lung (mg)	Heart (mg)	Kidney (mg)	Carcass (g)	Placenta (mg)
Hypoxia	162 ± 3	179 ± 5*	107 ± 4*	19.0 ± 0.7	21.4 ± 0.9*	1.78 ± 0.05*	501 ± 14
Control	169 ± 2	244 ± 9	123 ± 1	19.0 ± 0.5	27.0 ± 0.8	1.96 ± 0.03	504 ± 14

*$P < .01$, hypoxia *v* control.

Other mechanisms may contribute to the increased rGU. Plasma insulin concentrations were increased at the time of rGU measurements in both the maternal and fetal rats. Interestingly, this occurred despite normal maternal and fetal glucose concentrations on day 20 of gestation. The higher insulin concentrations may be the result of the transient increase in maternal (and probably fetal) glucose concentrations on days 17 and 18 or the direct effects of lactate, cortisol, and/or catecholamine on insulin secretion. Alterations in the fetal cardiovascular system during hypoxia may have influenced fetal heart rGU. Mean arterial pressure is elevated in hypoxic fetal sheep.[12] This might increase the workload and thus glucose requirements of the fetal heart. 2DG uptake and GLUT-1 expression of the adult rat heart are also increased following prolonged hypobaric hypoxia[13,14]; however, it is not certain whether this is a result of an increased workload or anaerobic metabolism.

In a previous study, we demonstrated increased rGU of fetal liver, muscle, kidney, and heart 2 days after maternal uterine artery ligation.[5] Uterine artery ligation, like maternal hypoxia, is associated with fetal hypoxia and acidosis. Although ligation limits fetal glucose availability, resulting in fetal hypoglycemia,[2,4] maternal hypoxia does not appear to alter fetal glucose concentrations or the fetal to maternal glucose ratio. Thus, this model offers an additional means to examine the effects of fetal hypoxia on fetal glucose metabolism. Although the degree of fetal hypoxia and acidosis produced by this model is similar to that occurring acutely after uterine artery ligation,[4] somewhat different effects on fetal tissue rGU were observed. Whereas heart and kidney rGU are increased in both models, liver and muscle rGU are not significantly affected by maternal hypoxia. These differences may be due to the longer duration of fetal hypoxia with the current model. Acute changes in tissue rGU that might have occurred following initiation of hypoxia may have resolved after 5 days of hypoxia.

Another rat model that produces IUGR is insulin-induced maternal hypoglycemia.[15] This model produces fetal hypoglycemia, but does not cause fetal hypoxia.[7] We have previously reported that maternal hypoglycemia of 2 or 5 days duration was associated with reduced rGU of fetal liver, lung, muscle, and kidney. rGU of fetal heart was also decreased after 2 days of hypoglycemia.[6] These findings are in contrast to those observed using the models of maternal hypoxia and uterine artery ligation, and therefore, they give further support to the premise that hypoxia has important effects on fetal glucose metabolism.

Brain growth is commonly "spared" during IUGR. This is probably achieved by an increase in cerebral blood flow,[16,17] allowing adequate nutrient and oxygen delivery to the fetal brain. Our data suggest that fetal brain growth is also spared during maternal hypoxia. We speculate that a compensatory increase in fetal cerebral blood flow also occurs with this model of IUGR, as it does with hypoxic fetal sheep,[18,19] thus allowing fetal brain to maintain normal rGU and growth.

Maternal exposure to varying degrees and durations of hypoxia has consistently been shown to produce IUGR in the rat or guinea pig.[20-23] Although previous studies have examined the effects of maternal hypoxia on fetal growth, little is known about the effects on fetal glucose homeostasis and metabolism. Our results indicate that exposure to 10% oxygen from day 15 through day 20 of gestation produces significant fetal growth retardation but does not alter the growth of fetal brain, heart, or placenta. Garvey and Longo[20] also demonstrated that maternal hypoxia did

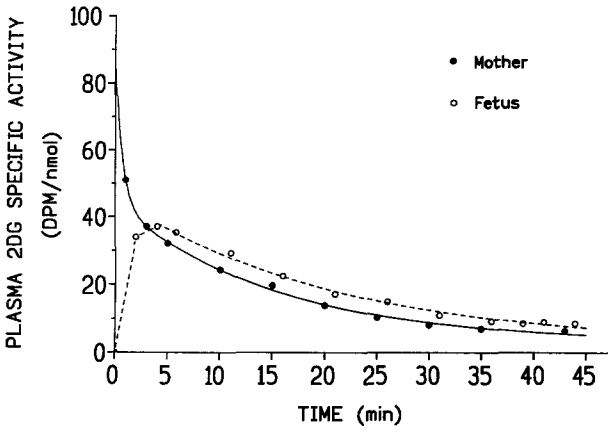

Fig 3. 2DG specific activity in maternal and fetal plasma after intravenous injection of [^{3}H]2DG into a representative maternal rat. The ratio of the areas under fetal and maternal curves is equivalent to P_k.

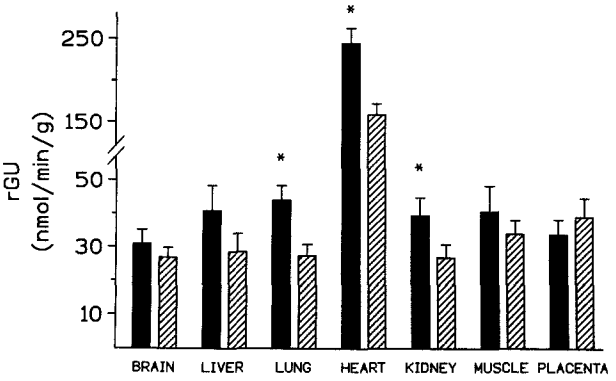

Fig 4. rGU of fetal tissues on day 20 of gestation following 5 days of maternal hypoxia (■) *v* control (▨). *$P < .05$, hypoxia *v* control. Nine control and 9 hypoxic rats were studied.

not affect fetal brain growth; however, Gilbert et al[21] and Van Geijn et al[22] did show a reduction in fetal brain mass following maternal hypoxia. However, hypoxia was initiated earlier in pregnancy and a greater degree of IUGR was observed in these two studies. In addition, these studies demonstrated that hypoxia had a lesser effect on brain growth than on body growth, and both studies showed an increase in brain to body weight ratios in hypoxic fetuses. As with our study, earlier studies have shown that hypoxia does not affect fetal heart[21] or placental[21,22] growth, but is associated with diminished fetal liver[20-22] and lung[23] weights.

The model of maternal hypoxia was used in the current study to assess further the effects of hypoxia on fetal tissue glucose utilization. It may not be the preferred model to represent the most common clinical condition resulting in IUGR, namely uteroplacental insufficiency. Uteroplacental insufficiency is likely caused by increased placental vascular resistance and reduced uteroplacental blood flow, resulting in not only fetal hypoxia but also fetal hypoglycemia. This combination of hypoxia and hypoglycemia has been documented in human growth-retarded fetuses.[24] The coexistence of hypoxia and hypoglycemia may have profound consequences. The increased demand for glucose due to anaerobic metabolism in conjunction with a limited glucose supply may severely compromise fetal growth and well-being. Indeed, uterine artery ligation appears to have a greater effect on fetal growth as compared with fetal hypoxia or fetal hypoglycemia alone.

We used a modification of Sokoloff's 2DG method to measure fetal tissue rGU.[8-10] An important limitation of this methodology is that only rGU rates can be determined. Measurements of *actual* glucose utilization must take into account differences in transport and phosphorylation rates that exist between 2DG and glucose. These differences, which are represented by the "lumped constant" in Sokoloff's original description, cannot be determined in fetal tissue.

The original 2DG methodology has been validated for brain and has been used in several other tissues. However, measurements of glucose utilization in tissues capable of glucogenesis, eg, liver, should be interpreted with caution. Glucose-6-phosphatase is capable of converting 2DG6P back to 2DG. Although glucose-6-phosphatase is present in rat liver and kidney, its activity is very low in fetal life[25,26] and would not likely affect rGU.

Measurement of rGU in fetal tissues requires the determination of P_k, which is the ratio of fetal to maternal 2DG specific activity. Alterations in maternal or fetal glucose metabolism or uterine blood flow may potentially influence P_k. However, maternal hypoxia did not affect P_k in this study.

This study highlights the importance of the effects of hypoxia on fetal glucose metabolism. Our results indicate that hypoxia causes an increase in glucose utilization of fetal lung, heart, and kidney. We speculate that this is primarily a result of increased glycolysis from anaerobic metabolism. Therefore, the effects of hypoxia on glucose metabolism must be considered when interpreting findings from other animal models of IUGR.

REFERENCES

1. Wigglesworth JS: Experimental growth retardation in the foetal rat. J Pathol Bacteriol 88:1-13, 1964
2. Oh W, D'Amodio MD, Yap LL, et al: Carbohydrate metabolism in experimental intrauterine growth retardation in rats. Am J Obstet Gynecol 108:415-421, 1970
3. Gilbert M, Leturque A: Fetal weight and its relationship to placental blood flow and placental weight in experimental intrauterine growth retardation in the rat. J Dev Physiol 4:237-246, 1982
4. Ogata ES, Bussey M, Finley S: Altered gas exchange, limited glucose and branched chain amino acids, and hypoinsulinemia retard fetal growth in the rat. Metabolism 35:970-977, 1986
5. Lueder FL, Ogata ES: Uterine artery ligation in the maternal rat alters fetal tissue glucose utilization. Pediatr Res 28:464-468, 1990
6. Lueder FL, Buroker CA, Kim SB, et al: Differential effects of short and long durations of insulin-induced maternal hypoglycemia upon fetal rat tissue growth and glucose utilization. Pediatr Res 32:436-440, 1992
7. Ogata ES, Paul RI, Finley SL: Limited maternal fuel availability due to hyperinsulinemia retards fetal growth and development in the rat. Pediatr Res 22:432-437, 1987
8. Sokoloff L, Reivich M, Kennedy C, et al: The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 28:897-916, 1977
9. Leturque A, Hauguel S, Kande J, et al: Glucose utilization by the placenta of anesthetized rats: Effect of insulin, glucose, and ketone bodies. Pediatr Res 22:483-487, 1987
10. Leturque A, Revelli JP, Hauguel S, et al: Hyperglycemia and hyperinsulinemia increase glucose utilization in fetal rat tissues. Am J Physiol 253:E616-E620, 1987
11. Girard J, Ferre P, Gilbert M, et al: Fetal metabolic response to maternal fasting in the rat. Am J Physiol 232:E456-E462, 1977
12. Kamitomo M, Longo LD, Gilbert RD: Right and left ventricular function in fetal sheep exposed to long-term high-altitude hypoxemia. Am J Physiol 262:H399-H405, 1992
13. Hurford WE, Crosby EG, Strauss HW, et al: Ventricular performance and glucose uptake in rats during chronic hypobaric hypoxia. J Nucl Med 31:1344-1351, 1990
14. Sivitz WI, Lund DD, Yorek B, et al: Pretranslational regulation of two cardiac glucose transporters in rats exposed to hypobaric hypoxia. Am J Physiol 263:E562-E569, 1992
15. Gruppuso PA, Migliori A, Susa JB, et al: Chronic maternal hyperinsulinemia and hypoglycemia. Biol Neonate 40:113-120, 1981
16. Arduini D, Rizzo G, Romanini C, et al: Fetal blood flow velocity waveforms as predictors of growth retardation. Obstet Gynecol 70:7-10, 1987
17. Wladimiroff JW, Van Den Wijngaard JAGW, Degani S, et al: Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies. Obstet Gynecol 69:705-709, 1987
18. Jones MD, Sheldon RE, Peeters LL, et al: Regulation of cerebral blood flow in the ovine fetus. Am J Physiol 235:H162-H166, 1978
19. Richardson BS, Carmichael L, Homan J, et al: Cerebral oxidative metabolism in fetal sheep with prolonged and graded hypoxemia. J Dev Physiol 19:77-83, 1993
20. Garvey DJ, Longo LD: Chronic low level maternal carbon monoxide exposure and fetal growth and development. Biol Reprod 19:8-14, 1978

21. Gilbert RD, Cummings LA, Juchau MR, et al: Placental diffusing capacity and fetal development in exercising or hypoxic guinea pigs. J Appl Physiol 46:828-834, 1979

22. Van Geijn HP, Kaylor WM, Nicola KR, et al: Induction of severe intrauterine growth retardation in the Sprague-Dawley rat. Am J Obstet Gynecol 137:43-47, 1980

23. Larson JE, Thurlbeck WM: The effect of experimental maternal hypoxia on fetal lung growth. Pediatr Res 24:156-159, 1988

24. Economides DL, Nicolaides KH: Blood glucose and oxygen tension levels in small-for-gestational-age fetuses. Am J Obstet Gynecol 160:385-389, 1989

25. Burchell A, Leakey JEA: Development of the rat hepatic microsomal glucose-6-phosphatase system and its glucocorticoid inducibility. Biol Neonate 54:107-115, 1988

26. Burch HB, Kuhlman AM, Skerjance J, et al: Changes in patterns of enzymes of carbohydrate metabolism in the developing rat kidney. Pediatrics 47:199-206, 1971