Compensation by Fetal Erythrocytes of Plasma Glucose Changes in Rats

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Changes in plasma glucose and glucose and glycogen content in fetal erythrocytes (FRBCs) were studied in rats between days 15 and 21 of gestation and in adult rats. Plasma and FRBC glucose concentrations increased during fetal life and were higher in erythrocytes than in plasma. Glycogen was higher in FRBCs than in adult erythrocytes and tended to decrease from day 15 to 19 of gestation and to increase again on day 21. When FRBCs were incubated in vitro in different glucose concentrations to study their capacity to compensate for changes in plasma glucose concentration, younger cells showed better glucose-buffering capacities. Glucose and glycogen levels in FRBCs increased when they were incubated in high-glucose medium, and the glycogen concentration reached was higher in the early fetal stage than by the end of gestation. Nevertheless, adult erythrocytes accumulated more glycogen in high-glucose medium than cells from any of the fetal-aged erythrocytes. When glucose was injected intraperitoneally into fetuses of different ages, there was an increase of 3.7 μM/ml in glucose concentration in blood from the umbilical artery and 2.5 μM/ml in blood from the umbilical vein. FRBCs buffered some of this change, as evident by an increase in glycogen content. Again, buffering capacity was greater for erythrocytes in younger fetuses. Epinephrine diminished glycogen concentration in venous FRBCs on days 19 and 21 of gestation even in hyperglycemia. Insulin diminished glucose concentration in arterial plasma on days 17 and 21 of gestation, but there were no changes in glucose and glycogen in FRBCs. FRBCs play an important role in glucose homeostasis, facilitating glucose transport in the placenta and increasing glucose delivery to other fetal tissues. *Diabetes* 39:1191–97, 1990

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Erythrocytes participate in the transport of the necessary elements for cellular respiration, which supplies the energy required for all other functions. Erythrocytes increase O_2 and CO_2 transport and regulate blood glucose levels (1). These cells absorb and incorporate glucose into their glycogen stores when glucose in plasma is high and release it when it is low (1). In the fetus, this function may be more evident, because all mammalian fetal erythrocytes (FRBCs) studied (except those of the cat) are permeable to glucose and contain more glucose-transporter molecules in their membranes than adult erythrocytes (2–4). It has even been proposed that the existence of high levels of glucose-transporter molecules is a characteristic of fetal blood (3).

The glucose-transporter system of FRBCs could increase the glucose pool in fetal blood and thereby facilitate glucose transfer from maternal to fetal blood in the placenta (5,6). In this study, we examined whether FRBCs have an increased capacity to compensate for changes in plasma glucose concentration. We further analyzed if insulin and epinephrine regulate the glucose-buffering function of FRBCs. We propose that the glucose-compensating capacity of FRBCs is a primitive mechanism for regulating glucose homeostasis that is later substituted by the hepatic and hormonal mechanisms of adults.

RESEARCH DESIGN AND METHODS

Experiments were done on 15-, 17-, 19-, and 21-day-old fetuses and 3-mo-old adult Wistar rats (from our colony). Gestation was verified 14 days after mating by abdominal palpation, and the fetal stage was determined according to the method of Jost and Picon (7).

Pregnant and adult animals were anesthetized with 30 mg/kg body wt i.p. pentobarbital sodium. Fetuses were exteriorized one by one, leaving the placenta in situ. Fetal blood samples from the umbilical cord were obtained with heparinized capillary tubes. For in vivo experiments, the umbilical

cord was ligated, and samples of blood from the umbilical artery and vein were obtained from each side of the ligature after cutting the cord. Blood from the fetus was collected first to avoid the effects of asphyxia. Adult blood was obtained by cardiac puncture.

Plasma glucose was determined by the glucose oxidase method with a Beckman analyzer (Fullerton, CA). Glucose and glycogen concentrations in FRBCs and adult erythrocytes and liver were determined by the acidic hydrolisis method of Passoneau and Lauderdale (8).

Plasma glucose and glucose and glycogen concentrations in FRBCs were measured in blood from the umbilical artery and vein. Each determination was repeated six times. The number of litters necessary to obtain enough blood varied according to age. Arterio-venous (A-V) differences were calculated. Analyses of variance (ANOVAs) were done to determine whether changes during fetal stages and the A-V differences were significant. Paired Student's *t* tests were used to determine whether A-V differences were statistically different from 0.

Glucose and glycogen concentrations and their total content in FRBCs were compared to those in the liver. For this comparison, body and liver weight, liver glucose and glycogen concentrations, and hematocrit were measured. Blood volume was considered to correspond to 12% of body weight (9).

In vitro experiments were done to determine the capacity of FRBCs to compensate for rises in plasma glucose concentration. Blood (0.2 ml) from different fetal ages or from adults was placed in each of six heparinized reaction tubes and centrifuged. Plasma was separated, and the buffy coat and superficial 1-mm layer of erythrocytes were removed and discarded. This method has been shown to be effective to separate erythrocytes from leukocytes in adult blood (1). Fetal blood contains circulating immature leukocytes and erythrocytes; nevertheless, the production of fetal leukocytes is minimal compared with erythrocytes (10). Our samples were examined microscopically and found to contain mostly (~90%) macrocytic nucleated erythrocytes and some reticulocytes and mature erythrocytes. Very few leukocytes were found. A similar cellular composition of fetal blood samples was previously reported (10). Plasma was then replaced with an equivalent volume of saline (0.9% NaCl) containing 0, 2.2, 4.4, 6.7, 8.9, and 11.1 μM/ml glucose concentrations. Erythrocytes were resuspended, incubated 15 min at 37.5–38°C and centrifuged (1).

To discriminate between the actual fetal state and high reticulocyte state per se, control experiments were done in three high-reticulocyte adult rats. Postbleeding reticulocytosis (95%) was used as a model. Blood was processed as in normal fetal blood. Additional experiments were done to determine if fetal and adult erythrocytes were able to release glucose into the medium. In these experiments, erythrocytes were preincubated in solution of 5% glucose in saline (277.7 mM glucose) to replenish glycogen stores, followed by incubation in saline with no glucose. Glucose in the supernatant and glucose and glycogen in erythrocytes were determined. Control samples were resuspended and incubated in their own plasma. Each experimental sample was repeated six times with the number of litters necessary to obtain enough blood. ANOVA was used to evaluate the differences among fetal ages and between different glucose concentrations in the in vitro experiments.

For in vivo experiments, glucose (400 μg/100 g expected body wt diluted in 25–50 μl saline), epinephrine (Fustery, Mexico City, Mexico; 2 μg/100 g expected body wt diluted in the same volume of saline), or insulin (Lilly, Indianapolis, IN; 0.1 U/100 g expected body wt diluted in the same volume of distilled water) were injected in the peritoneum of half of the fetuses of each litter. The rest of the fetuses were used as controls and received no injection. There were no differences between saline-injected fetuses and fetuses that received no injection. Injections were made through the wall of the uterine horn with a 27-gauge needle, and the uterus was returned to the abdominal cavity. Fifteen minutes were allowed for hormones and glucose to act. We found that 15 min is enough time to see the effects of insulin and epinephrine on liver glycogen in fetuses of different ages (unpublished observations). Blood from the umbilical artery and vein was collected. Glucose in plasma and glucose and glycogen in FRBCs were determined. Student's *t* test was

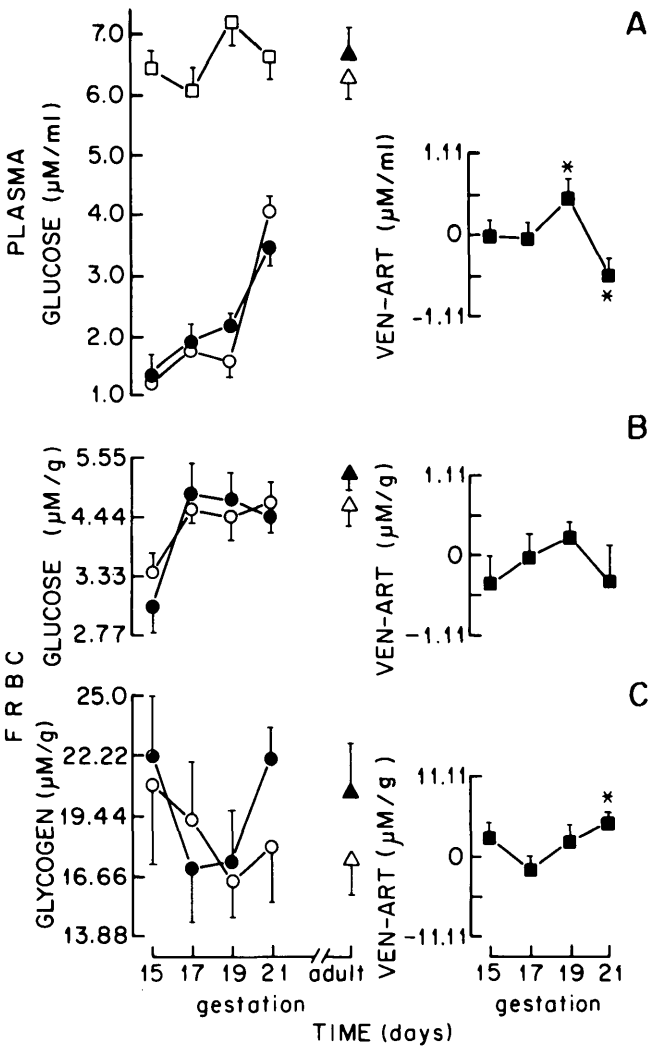

FIG. 1. Levels of plasma glucose (*A*), fetal erythrocyte (FRBC) glucose (*B*), and glycogen (*C*) in erythrocytes during development. ●, Blood from umbilical vein; ○, blood from umbilical artery; ▲, adult femoral arterial blood; △, adult femoral venous blood; □, maternal blood; ■, arteriovenous (VEN-ART) difference. *Vertical bars* represent SE. Each data *point* represents mean of 6 experiments. *$P < 0.05$.

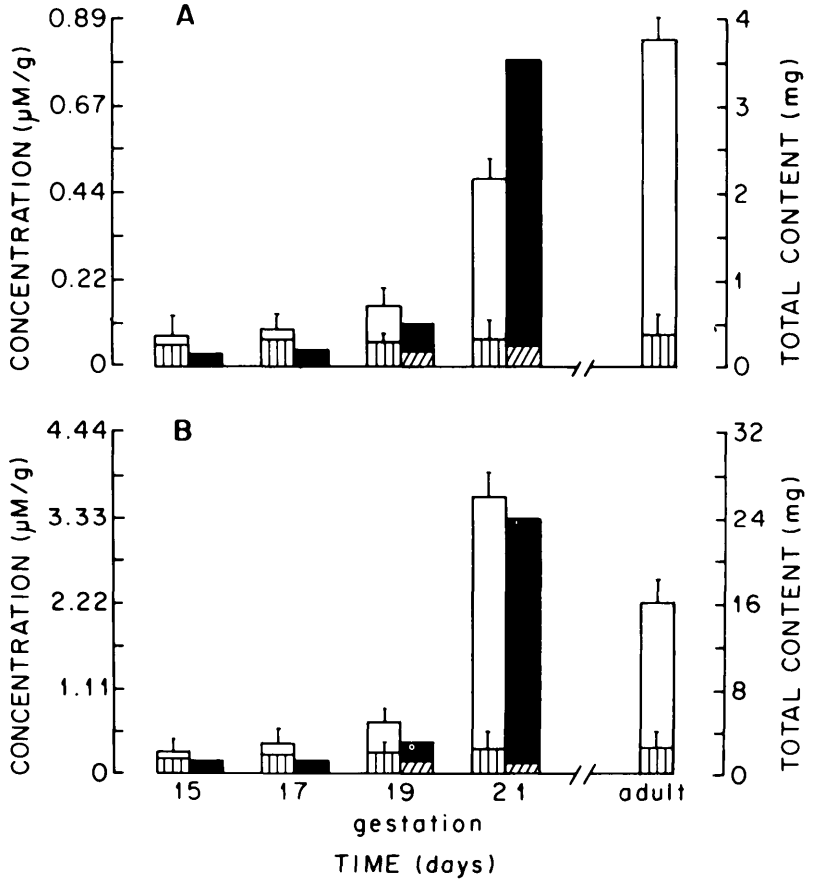

FIG. 2. Changes in total content and concentration of glucose (*A*) and glycogen (*B*) in fetal erythrocytes (▨, total content; ▥, concentration) and liver (■, total content; □, concentration) during rat fetal development and in adult rat.

used to evaluate the differences between injected and control samples.

RESULTS

From day 15 to 19 of gestation, plasma glucose from the umbilical vein and artery was low (1.7 μM/ml) compared with adult levels. Plasma glucose rose sharply to 3.9 μM on day 21 ($P < 0.001$; Fig. 1*A*). No significant A-V glucose differences were found on days 15 and 17. On day 19, glucose concentration in blood from the vein was higher than in blood from the artery. In contrast, on day 21, glucose concentration in the artery rose above levels in the vein (Fig. 1*A*).

Glucose concentration in FRBCs from the vein and from the artery was 3.0–3.6 μM/ml on day 15 and increased on day 17 to maintain a level around 4.4–4.7 μM until the end of gestation ($P < 0.01$; Fig. 1*B*). Glucose in FRBCs was always higher than plasma glucose. A-V glucose difference in FRBCs was close to 0 throughout the study period.

Glycogen in FRBCs from the artery and from the vein decreased between days 15 and 19 to increase again on day 21 ($P < 0.05$). On day 21 of gestation, glycogen in FRBCs from the vein was significantly higher than FRBCs from the artery ($P < 0.05$). Glycogen difference rose significantly on day 21 ($P < 0.05$; Fig. 1*C*).

The stores of glucose and glycogen in FRBCs were comparable to those in hepatocytes early in fetal life (days 15 and 17). However, on days 19 and 21 of gestation, glucose and glycogen in cells from the liver (expressed as concentration or total content) increased when compared with erythrocytes (Fig. 2).

To determine the capacity of FRBCs to compensate for increases in plasma glucose concentration, we incubated these cells in vitro with different concentrations of glucose. Figure 3 shows that erythrocytes were able to absorb glucose when the glucose concentration in the medium was high ($P < 0.001$). The higher the concentration of glucose in the medium, the more glucose was taken up by the FRBCs. This response was approximately linear until saturation was reached; this happened at different concentrations for the different ages. The capacity for glucose uptake was highest in day 15 FRBCs and tended to decrease during development ($P < 0.001$). Adult erythrocytes had the least capacity to compensate for increases in glucose concentration (Fig. 3*A*). In control experiments, reticulocytes showed a slight increase (not significant) in their capacity to compensate for high glucose concentrations in relation to normal erythrocytes, but the response was significantly lower ($P < 0.001$) when compared with FRBCs of all the ages studied; the mean changes obtained in the supernatant glucose were +0.6, −0.7, −1.1, −1.7, −2.8, and −2.3 μM/ml when glucose concentration in the medium before incubation was 0, 2.2, 4.4, 6.7, 8.9, and 11.1 μM/ml, respectively (compare with the results in Fig. 3*A*).

Glucose levels inside FRBCs increased when glucose in the medium rose ($P < 0.001$). However, this increase could not explain the capacity of FRBCs to deplete the medium of glucose; furthermore, there were no significant differences in glucose levels among FRBCs from the different fetal ages (Fig. 3*B*). We previously showed that erythrocytes store glucose in the form of glycogen (1). Therefore, we tested if glycogen in FRBCs increased when incubated in high-glu-

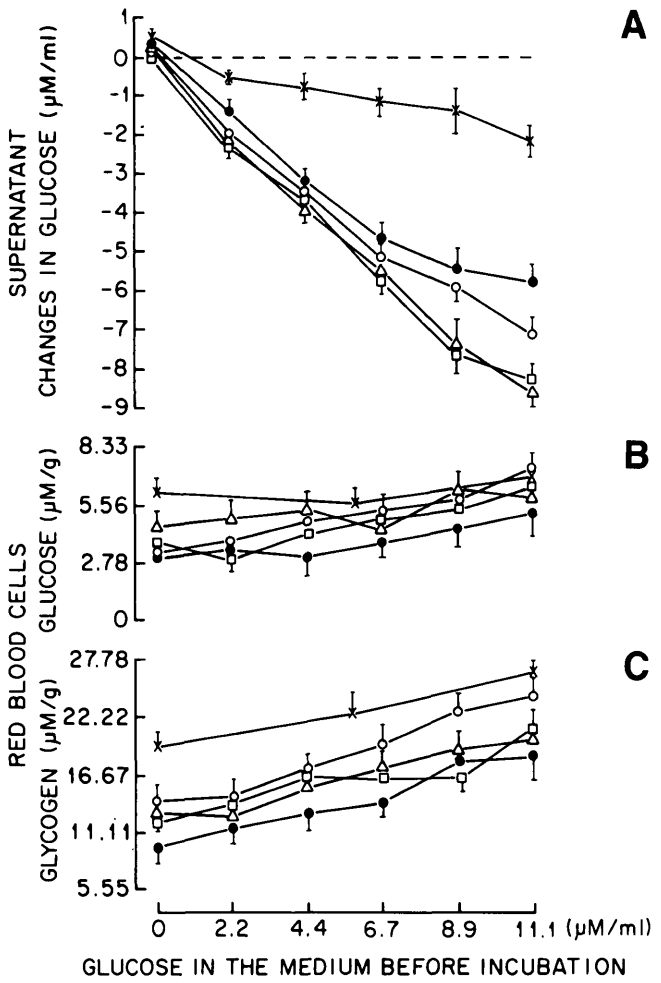

FIG. 3. Effect of graded glucose concentration on fetal erythrocytes (FRBCs). Glucose in incubation supernatant (*A*) and glucose (*B*) and glycogen (*C*) in FRBCs were measured 15 min after exposure to different glucose concentrations. △, Day 15; □, day 17; ○, day 19; ●, day 21; X, FRBCs and adult erythrocytes.

cose medium. Figure 3C shows that this was the case. There was a linear relationship between glucose in the medium and glycogen stores ($P < 0.01$). Day 21 FRBCs stored the least glycogen. Yet, the youngest FRBCs (day 15) were not the ones with the greatest increase in their glycogen stores. Adult erythrocytes showed the highest capacity to store glycogen (Fig. 3C). It is interesting that glycogen values after incubation in low-glucose medium were below basal values in all ages studied and rose above basal values when they were incubated in high-glucose medium (compare Figs. 1C and 3C).

Experiments in vitro after preincubating erythrocytes in a high-glucose medium showed that FRBCs release 0.5 times more glucose than adult erythrocytes. Glucose in FRBCs that did not change without the preincubation period increased in day 17 erythrocytes 10 times more than in the adults. Glycogen in erythrocytes that had already tended to decrease without the preincubation period decreased in day 17 erythrocytes 0.7 times more than in the adult erythrocytes (Table 1).

Fetal glucose injections increased plasma glucose concentration in blood from the umbilical vein and the umbilical artery ($P < 0.05$). This increase was higher in day 17 fetuses than in day 21 fetuses. FRBC glucose and glycogen levels were not modified in arterial blood but increased significantly in venous blood ($P < 0.05$). Again, the increase was greater in day 17 fetuses than in day 21 fetuses (Table 2).

Epinephrine only had effects on venous blood in which plasma glucose concentration rose significantly on days 19 and 21 ($P < 0.05$), and glycogen concentration decreased on day 21 even during hyperglycemia ($P < 0.05$; Table 2). Insulin had no significant effects on venous plasma glucose concentration or on glucose and glycogen levels in FRBCs in any of the ages studied. Slight but significant decreases in arterial plasma glucose were observed on days 17 and 21 (Table 2).

DISCUSSION

Erythrocytes of most mammalian species participate not only in O_2 and CO_2 transport but in glucose transport as well (1). Although FRBCs contain more glucose-transporter molecules in their membranes than adult erythrocytes (3,4), the physiological role of these molecules in FRBCs remains unknown. In this study we analyzed the capacity of rat FRBCs to compensate for changes in glucose concentration in plasma. During the fetal stage in the rat, blood is composed primarily of macrocytic nucleated precursors of erythrocytes. Few reticulocytes, mature erythrocytes, or leukocytes are present. The composition of the blood in the rat fetuses would probably correspond to the pattern of hepatic hemopoiesis found in the human fetus at about one-third of gestation (10). Our results indicate that FRBCs participate in glucose homeostasis and may facilitate glucose transport to fetal blood in the placenta and help in the delivery of glucose to other tissues.

Plasma glucose concentration increased during fetal development. Because glucose crosses the placenta by a process of facilitated diffusion (11) and maternal blood glucose did not change, finding an increase in fetal blood glucose was unexpected. This increase could due to *1*) the existence of regulatory mechanisms of placental metabolism capable of modifying how much glucose gets through the placenta as suggested by Shambaugh et al. (12) and Ramsay et al. (13), who found that, by the end of gestation, the placenta consumes more lactate, allowing more glucose to reach the fetus; *2*) an increase in the number of glucose-transporter molecules in the placenta at the end of gestation; *3*) glucose release within the fetus through the glycogenolytic pathways (1,14,15), that is, the activity of the enzymes involved in these pathways increase to near adult levels at the end of gestation; and *4*) a decrease in the capacity of FRBCs to absorb glucose from plasma at the end of the fetal stage as suggested by Jacquez (3) and by the results presented herein.

Maternal blood glucose was always higher than blood glucose in the fetuses. This had been previously described for other species as well (16). The higher capacity of FRBCs to absorb glucose from plasma, thus maintaining the glucose concentration gradient from maternal to fetal blood, might explain this observation.

From days 15 to 19 of gestation, no significant A-V glucose differences were detected. On day 21, however, glucose concentration in venous blood rose above that in arterial blood. These results suggest that blood glucose retention

TABLE 1
Capacity of fetal erythrocytes (FRBCs) and adult erythrocytes to liberate glucose to nonglucose medium with and without high-glucose (276.7 mM) preincubation period

	Gestation (days)			
	17	19	21	Adult
Glucose in medium (μM/ml)				
No preincubation				
Before incubation	0 (6)	0 (6)	0 (6)	0 (6)
After incubation	0.19 ± 0.02 (6)	0.16 ± 0.03 (6)	0.25 ± 0.04 (6)	0.87 ± 0.09 (6)
Mean change	0.19	0.16	0.25	0.87
Preincubation				
Before incubation	0 (3)	0 (3)	0 (6)	0 (6)
After incubation	34.67 ± 0.63 (3)	28.89 ± 2.93 (3)	35.03 ± 0.41 (6)	21.43 ± 1.10 (6)
Mean change	34.67	28.89	35.03	21.43
Glucose in FRBCs (μM/g)				
No preincubation				
Before incubation	4.82 ± 4.43 (6)	5.33 ± 0.28 (6)	4.09 ± 0.43 (6)	7.33 ± 0.67 (6)
After incubation	4.82 ± 0.34 (6)	4.82 ± 0.39 (6)	4.63 ± 0.55 (6)	7.11 ± 0.24 (6)
Mean change	0	−0.52	0.56	−0.22
Preincubation				
Before incubation	156.67 ± 2.98 (4)	94.77 ± 6.23 (3)	86.11 ± 4.76 (3)	34.05 ± 4.03 (6)
After incubation	40.56 ± 6.11 (3)	35.56 ± 3.57 (3)	50.03 ± 3.38 (3)	21.83 ± 1.11 (13)
Mean change	−116.11	−59.26	−36.08	−12.18
Glycogen in FRBCs (μM/g)				
No preincubation				
Before incubation	21.66 ± 1.63 (6)	18.22 ± 2.96 (6)	19.07 ± 0.66 (6)	26.03 ± 3.23 (6)
After incubation	12.78 ± 1.41 (6)	13.71 ± 1.79 (6)	10.18 ± 1.16 (6)	19.58 ± 4.08 (6)
Mean change	−8.89	−4.52	−8.89	−6.47
Preincubation				
Before incubation	32.22 ± 8.28 (4)	40.37 ± 3.76 (3)	42.22 ± 3.89 (3)	38.11 ± 1.76 (6)
After incubation	17.78 ± 3.88 (4)	31.15 ± 0.64 (3)	33.33 ± 3.06 (6)	29.67 ± 1.34 (10)
Mean chage	−14.44	−9.26	−8.92	−8.48

Values are means ± SE for *n* determinations (in parentheses).

by fetal tissues was low. Alternatively, glucose retention was being overshadowed by glucose release through glycogenolysis from tissue reserves. In accordance with the first interpretation, other authors have found that glucose cannot account for the total O_2 consumption or meet C requirements of new tissue accretion, suggesting that other substrata may be used (17). Lactate (11,18,19), fructose (17,20), galactose (11), acetate (19), pyruvate (18), and amino acids such as alanine or glutamate (21) have been suggested.

Glucose concentration in FRBCs increased during fetal development and was always higher than in plasma. In contrast, in adult blood, most glucose is found in plasma (22). Similar results on the plasma glucose–FRBC glucose ratio were previously reported (23). Moreover, there have been some reports of higher glucose concentrations in plasma than in FRBCs (2).

Glycogen in FRBCs decreased from days 15 to 19 of gestation, and at these times, the A-V glucose difference was low. Glycogen concentration in FRBCs increased on day 21 and the A-V glucose difference rose. Similar changes were observed in glycogen concentration in other fetal organs such as brain and kidney (unpublished observations), which also suggests a change in glucose homeostasis from tissue-specific self-regulation to integrated regulation.

Glucose and glycogen stores in circulating FRBCs were almost equal to those in liver cells early in fetal life. In near-term fetuses, the liver became a carbohydrate store, and the levels of glucose and glycogen in FRBCs were much less than those in hepatocytes. However, the relative weight of the liver with respect to total body weight is very high at the beginning of fetal development, when it is not playing an important role as a carbohydrate store, and decreases by the end of gestation (22). The fetal liver might be in charge of glucose homeostasis producing and releasing FRBCs (7,10) before becoming a carbohydrate store. These cells may serve as transport and buffer for glucose. In the placenta, they replenish their glycogen stores to transport and release glucose to other tissues.

When FRBCs of different ages were incubated in vitro in high glucose concentrations, those of earlier stages of gestation had greater glucose-buffering capacities. The glucose and glycogen levels in FRBCs increased when the cells were incubated in high-glucose medium. FRBCs from day 21 accumulated less glycogen; however, the glycogen concentration in day 15 erythrocytes was not the highest. This was probably because we measured the glycogen in FRBCs of the different ages in fixed volume of erythrocytes, without considering that day 15 erythrocytes are macrocytic and nucleated, whereas those at the end of gestation have already lost their nuclei (10). Therefore, the cytosolic capacity of erythrocytes varies with the age of erythrocytes. It was unexpected to find that adult erythrocytes, which absorbed the least glucose from the medium, were the cells that most increased their glycogen stores. Glucose absorbed from medium by FRBCs might not only be stored but might be actively used for metabolism in a greater proportion in fetal cells than in adult cells. This interpretation may be supported by the increase in glycogen in adult cells being of about the

TABLE 2
Effects of intraperitoneal injections of glucose, epinephrine, and insulin on fetuses of different ages

	Gestation (days)		
	17	19	21
Plasma glucose (μM/ml)			
Control			
Venous	2.06 ± 0.35	2.38 ± 0.29	2.29 ± 0.22
Arterial	2.06 ± 0.28	1.59 ± 0.19	2.81 ± 0.32
Glucose			
Venous	4.58 ± 0.65*	4.27 ± 0.33*	3.38 ± 0.22
Arterial	5.72 ± 1.10*	5.16 ± 0.33*	5.72 ± 0.64*
Epinephrine			
Venous	2.70 ± 0.56	2.34 ± 0.21	2.42 ± 0.19
Arterial	2.63 ± 0.31	2.04 ± 0.22*	3.73 ± 0.38
Insulin			
Venous	2.49 ± 0.35	1.92 ± 0.31	1.94 ± 0.40
Arterial	2.74 ± 0.28	1.72 ± 0.24	2.59 ± 0.39
FRBC glucose (μM/g)			
Control			
Venous	4.76 ± 0.57	4.67 ± 0.38	4.61 ± 0.34
Arterial	4.76 ± 0.29	4.56 ± 0.33	4.78 ± 0.31
Glucose			
Venous	5.24 ± 0.37	5.0 ± 0.34	4.28 ± 0.35
Arterial	6.98 ± 0.59*	7.08 ± 0.48*	5.72 ± 0.51
Epinephrine			
Venous	3.97 ± 0.21	4.78 ± 0.39*	4.86 ± 0.39
Arterial	4.28 ± 0.27	4.33 ± 0.29	5.14 ± 0.55
Insulin			
Venous	4.44 ± 0.22	4.58 ± 0.42	4.61 ± 0.35
Arterial	4.29 ± 0.36	5.14 ± 0.39	4.92 ± 0.21
FRBC glycogen (μM/g)			
Control			
Venous	17.46 ± 1.61	17.56 ± 2.02	21.88 ± 1.50
Arterial	16.77 ± 2.38	16.75 ± 1.56	19.03 ± 1.56
Glucose			
Venous	17.78 ± 1.62	20.0 ± 2.90	20.63 ± 1.65
Arterial	23.94 ± 1.57*	20.0 ± 1.86*	21.98 ± 2.31
Epinephrine			
Venous	18.41 ± 1.68	16.33 ± 2.16	21.81 ± 2.18
Arterial	16.51 ± 1.18	17.33 ± 1.83	16.53 ± 1.42
Insulin			
Venous	12.86 ± 1.47*	18.33 ± 2.53	19.05 ± 1.60*
Arterial	18.73 ± 1.41	17.78 ± 1.89	20.48 ± 1.14

Values are means ± SE of 6 experiments. FRBC, fetal erythrocytes; venous, umbilical vein; arterial, umbilical artery.
*$P < 0.05$.

same magnitude as the increase for fetal cells, even though the glucose consumption is much less for the adult cells (Fig. 3C). FRBCs released glucose and diminished their glycogen stores more readily than adult erythrocytes when incubated in low glucose concentrations after replenishing their glycogen stores. The data on the capacity of FRBCs to compensate for increases and decreases in glucose concentration in plasma agree with the results of Goodwin (2) and Kondo and Beutler (4), who suggest that, with maturation, erythroblasts lose a proteinaceous membrane component that could correspond to the glucose-transporter molecule.

When glucose was injected intraperitoneally to fetuses of different ages, erythrocytes were capable of buffering the increase in glycemia from the earlier fetal age studied (day 17). Nevertheless, by the end of gestation, changes in glycemia were less important. This was probably due to the establishment of new and more effective mechanisms for controlling glucose homeostasis, such as the differentiation of the liver as a carbohydrate store (22).

Epinephrine diminished glycogen concentration in FRBCs on day 21 of gestation even in hyperglycemia. In this respect, day 21 and adult erythrocytes behaved as circulating hepatocytes (1). Such an effect was not observed in FRBCs from days 17 and 19 of gestation, suggesting that hormonal control in the fetus might be very different from the adult. Similarly, insulin did not modify the glucose-buffering capacity of FRBCs on any of the ages studied as it does in adult erythrocytes (1). Although it has been reported that adult reticulocytes have insulin receptors that are lost on maturation (24,25) and β-adrenergic receptors (26), there are no reports on the existence of insulin or epinephrine receptors in FRBCs.

We conclude that FRBCs and not reticulocytes have a high capacity to compensate for changes in glucose concentrations. This capacity is partially lost by adult erythrocytes. The glucose-buffering function of FRBCs might facilitate glucose transport into fetal blood from the placenta by providing a larger fetal blood glucose capacity. FRBCs may also serve as glucose carriers increasing the efficiency of glucose de-

livery to other fetal tissues. Therefore, these cells are important in fetal glucose homeostasis, particularly at the beginning of the fetal stage, in which the liver has not yet differentiated as a glycogen store.

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