Postmaturity in the Rat: Glucose Metabolism in the Fetus and the Neonate

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Summary

The present study was designed to investigate glucose metabolism in the postmature fetus and newborn. In the fetus, the decreased hepatic glycogen content together with the decrease by the same percentage of total hepatic glycogen radioactivity from directly injected [6-³H]glucose demonstrate that fetal glycogenolysis occurs during prolonged gestation. Moreover, fetal glycogen synthesis as tested by *in vivo* [6-³H]glucose incorporation experiments is inhibited. *In vivo* experiments with [¹⁴C]lactate are consistent with gluconeogenesis, being inactive in the postmature fetus as well as in the normal-term fetus. During the first hr after delivery, our *in vivo* data about conversion of [¹⁴C]lactate to glucose show that the gluconeogenic pathway is not functioning in spite of very high phosphoenolpyruvate carboxykinase activity in the postmature. By 3 hr postpartum, the phosphoenolpyruvate carboxykinase activity, the blood lactate level, the percentage of conversion, and the rate of gluconeogenesis are very elevated in the postmatures as compared to the term neonates. By 6 hr postpartum, despite maintained phosphoenolpyruvate carboxykinase activity, gluconeogenic rate becomes very weak in postmatures kept fasting. This is the time characterized by a profound hypoglycemia. In contrast, fed postmature neonates exhibit normal blood glucose levels by 6 and 12 hr postpartum as a result of sustained rate of gluconeogenesis.

Speculation

In utero hepatic glycogenolysis of the postmature rat leads to impaired capacity to cope with neonatal fasting. Gluconeogenic pathway, as measured under normal blood oxygenation of the mother, is not operating in the postmature as well as in the term fetus.

In the normal-term fetus, the metabolic state may be considered as one of maximal anabolism and glucose in the fetus has been claimed to be entirely maternal in origin (4, 11).

In a previous study (25), blood glucose level in the postmature fetal rat was found to be the same as in the normal-term fetus. However, as suggested by some recent data (27, 33), near term and during prolonged gestation the placenta begins to suffer a progressive loss of function, and as a consequence, limitation of transplacental supply of maternal glucose may be of importance. Therefore, the question about origin of glucose in the postmature fetus is raised. The decreasing hepatic glycogen contents observed in the postmature fetus (25) can account for a possible source of fetal glucose during prolonged gestation. Moreover, several lines of evidence are consistent with fetal hepatic gluconeogenesis being induced by prolonged gestation: (1) the insulin fall and glucagon rise in the plasma (24) are appropriate to the appearance of fetal hepatic gluconeogenesis (10, 22, 35); (2) the prerequisites of increased activity of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase (PEPCK) occur (23) analogous to the changes seen postnatally (10).

The present study has been performed to investigate *in vivo* the liver glycogen synthesis, degradation, and the gluconeogenesis in postmature fetuses. Besides, we have shown that the postmature newborn has very low glycogen stores and develops acute and sustained postnatal hypoglycemia when maintained fasted (25). Therefore, it was of interest to determine the rate of functioning of the gluconeogenic pathway and the effect of suckling on the glycemic status in these animals.

MATERIALS AND METHODS

ANIMALS

Albino rats (Sherman strain) receiving pelleted commercial chow were used. Females were caged with a male for one night (5 PM to 9 AM) and recognized pregnant by abdominal palpation 14 days later.

EXPERIMENTAL PROCEDURES

The procedure used to prolong gestation with progesterone has been previously described (25). It has been checked that progesterone *per se* has no effect on the different parameters studied. Postmature fetuses (23.5 days old) were compared to term 21.5-day-old fetuses. To study *in vivo* gluconeogenesis, two fetuses in each litter were given injections IV through the vitelline vein (17) with 3 μ Ci of L-[U-¹⁴C]lactate (Amersham, Buckinghamshire, United Kingdom) (50 mCi/mmol) in 50 μ l saline. In other experiments designed to study glycogen synthesis and breakdown, five fetuses per litter were given injections SC through the uterine wall with 5 μ Ci of D-[6-³H]glucose (Amersham) (15 Ci/mmol) in 20 μ l saline. All the injection experiments were performed while the mother was under pentobarbital (4 mg/100 g body weight) anesthesia. In all experiments, the control fetuses received the same amount of saline as did the injected fetuses.

For study of neonatal gluconeogenesis, newborns were given injections IP at birth with 1 μ Ci of L-[U-¹⁴C]lactate in 50 μ l solution.

For sampling, fetuses were successively extracted from the uterus, leaving placenta and umbilical cord *in situ* while the mother was anesthetized. Term newborns were obtained by cesarean section on day 21.5 postconception (p.c.), and postmature newborns were obtained by cesarean section on day 23.5 p.c. They were kept fasted for 6 hr at 36°C. In another experimental protocol, the rats were left with foster mother and began suckling at about 4 hr. Blood glucose was collected from the axillary vessels, and livers were rapidly removed, weighed, and submitted to enzyme or glycogen determinations. Maternal blood was sampled from the carotid artery.

Incorporation of [³H]Glucose into Fetal Liver Glycogen. The glycogen present in the liver of postmature or term fetuses was labeled by injecting a trace amount of [6-³H]glucose into the fetuses at 19.5 days p.c. The radioactivity incorporated in the glycogen was determined 1 hr, and 1, 2, 3, and 4 days after the administration of the label. The glycogen was extracted by the

method of Stetten *et al.* (31). Results are expressed as amount of ^3H in 100 mg liver glycogen (cpm/100 mg glycogen) and as amount of ^3H in total liver glycogen (cpm per liver).

In the same experiments, we determined total ^3H radioactivity and [^3H]glucose radioactivity present in fetal and maternal blood. The quantity of [^3H]glucose remaining in the blood at any time of the experiment was measured after the evaporation of the blood water; [^3H]H₂O is the main but nonionic metabolic product of [6- ^3H]glucose (18), so there is a slight overestimation of the [^3H]glucose in the blood.

$$\% \text{ } ^3\text{H} \text{ glucose} = 100 \times \frac{[\text{ } ^3\text{H} \text{ glucose (cpm/ml)}]}{\text{total } ^3\text{H (cpm/ml)}}$$

Gluconeogenic Rate in the Newborn. Blood was sampled at intervals (30 min in the fetuses; 30 min, and 3, 6, and 12 hr in the neonates) after the injection of the labeled precursor. The samples were immediately deproteinized with methanol, and filtrates were analyzed for labeled glucose. To separate labeled glucose from labeled lactate and others labeled metabolites, glucose was precipitated as kalium gluconate according to Malimovka (19). During radioactivity measurements, appropriate corrections were made to take into account the following parameters: (1) quenching because 0.3 N HNO₃ was used to dissolve kalium gluconate; (2) recovery of glucose because gluconate was always less than 100% (92 to 98%). The value was determined in every experiment by measuring the percentage of recovery of added glucose; (3) some radioactivity was found in the gluconate fraction when the blood was taken immediately after lactate injection, *i.e.*, before any synthesis of glucose. This contamination of the gluconate fraction by the lactate was about 2%. In the neonate, the percentage of injected [^{14}C]lactate converted to labeled glucose in 30 min was calculated on the basis of an assumed average glucose space of 60% of body weight in the newborn rat (29).

$$\% \text{ conversion to glucose} = 100 \times \frac{\text{glucose space (ml)} \times [\text{ } ^{14}\text{C} \text{ glucose in blood (cpm/ml)}]}{\text{administered radioactivity (cpm)}}$$

The rate of gluconeogenesis from lactate was calculated by multiplying the percentage conversion to glucose by the lactate pool assuming that 2 molecules of lactate gave one molecule of glucose. Lactate pool was calculated on the basis of a lactate space assumed to equal the total body water, *i.e.*, 80 ml/100 g body weight (30)

$$\begin{aligned} \text{Gluconeogenesis rate } (\mu\text{moles glucose/hr/100 g body weight}) \\ = \% \text{ conversion to glucose in 1 hr} \\ \times \frac{\text{lactate pool } (\mu\text{moles})}{2} \times \frac{\text{body weight (g)}}{100} \end{aligned}$$

In Vivo Gluconeogenesis in the Fetus. This calculation was not applicable to the fetuses which, in contrast to the newborn, are connected to the maternal compartments so that the labeled precursor passes from the fetuses given injections into the maternal circulation where it is converted into other compounds and passes back into all the fetuses. As a matter of fact, ^{14}C -labeled compounds are rapidly found in the control fetuses given injections only with saline, and the radioactivity present in the fetuses given injections with [^{14}C]lactate has a double origin: it comes first from ^{14}C label injected directly and second from the ^{14}C label coming back from the maternal circulation. If one considers that the radioactivity originating from the mother is distributed equally between all the fetuses of the litter, it is possible to evaluate in the fetus given an injection with the labeled precursor the radioactivity of maternal origin (which is the same as the radioactivity measured in a control fetus given an injection with saline) and to subtract its value from total radioactivity. The percentage of ^{14}C as glucose in fetuses given injections with [^{14}C]lactate is calculated as follows

$$100 \times \frac{\begin{aligned} &\text{cpm } ^{14}\text{C} \text{ glucose/ml} \\ &(\text{fetus given an injection with lactate}) - \\ &\text{cpm } ^{14}\text{C} \text{ glucose/ml (control fetus)} \end{aligned}}{\begin{aligned} &\text{cpm } ^{14}\text{C} \text{ total/ml} \\ &(\text{fetus given an injection with lactate}) - \\ &\text{cpm } ^{14}\text{C} \text{ total/ml (control fetus)} \end{aligned}}$$

OTHER BIOCHEMICAL PROCEDURES

Blood glucose was measured by the glucose-oxidase method (15). Lactate was determined in blood filtrate by an enzymic microfluorometric method (20). Glycogen was measured after conversion into glucose by Amylo-1-4,1-6 glucosidase according to the method of Roebling and Allred (26).

Glucose-6-phosphatase (EC 3.1.3.9) was estimated in crude homogenates with the method of Swanson (32). Activity of glucose-6-phosphatase is reported as $\mu\text{moles P}_i$ release per min per protein at 37°C. Soluble PEPCK (EC 4.1.1.32) from the 100,000 $\times$ g supernatant of the homogenates was measured by the method of Ballard and Hanson (1). Activity is reported as nmoles of ^{14}CC from NaH $^{14}\text{CO}_3$ (Amersham) fixed per min per g protein at 37°C. Inorganic phosphate was assayed by the procedure of Chen *et al.* (6). Proteins were determined by the biuret method (14).

All the results are expressed as mean $\pm$ S.E. Calculations of statistical significance of differences between the groups were performed by the Student *t* test for unpaired data.

RESULTS

SYNTHESIS OF GLYCOGEN FROM GLUCOSE AND DEGRADATION OF GLYCOGEN IN THE FETAL LIVER

Evolution of [^3H]Glucose Radioactivity Present in the Blood of Fetuses and Mothers. After injection of [6- ^3H]glucose to fetus on day 19.5 p.c., the value of cpm [^3H]glucose recovered per 100 mg fetal blood 60 min later was about 2000 cpm/100 mg and there after decreased sharply up to day 20.5 (Table 1). Values observed from day 21.5 p.c. onward suggest that from this date incorporation of labeled glucose into glycogen is negligible because the quantity of radioactive glucose units present in the fetal blood is very low.

Results obtained from the mothers indicate that the labeled glucose injected to fetuses crosses the placenta and appears in maternal blood. The value obtained for [^3H]glucose per 100 mg maternal blood is maximal between 15 and 30 min after the injection, and 24 hr later, it may be considered as negligible.

Evolution of [^3H]Glucose Radioactivity Present in the Liver Glycogen of the Fetus and the Mother. From days 19.5 to 21.5 p.c. specific radioactivity of fetal liver glycogen decreases (Table 2). This is related to dilution of glycogen labeled after [6- ^3H]glucose injection with unlabeled glycogen because during this period fetal liver accumulates glycogen at a high rate (16). In contrast, specific radioactivity of glycogen is maintained between days 21.5 and 23.5 p.c. Inasmuch as specific radioactivity of blood glucose is very low during this period, one may admit that glycogen synthesis is not operating during this period. This conclusion was confirmed by experiments in which 23.5-day-old fetuses were given injection SC with [6- ^3H]glucose (5 μCi): no incorporation of [^3H]glucose into glycogen was observed 60 min after the injection.

Moreover, there is no significant difference between the total radioactivity present in liver glycogen on days 20.5 and 21.5. This

Table 1. Time course of [^3H]glucose radioactivity in the fetal and maternal bloods after the injection of D-[6- ^3H]glucose to fetuses on day 19.5 p.c.

Day p.c.	Time after injection	cpm [^3H]glucose/100 mg blood	
		Mother	Fetus
19.5	5 min	959 $\pm$ 284 ¹ (4) ²	
19.5	15 min	2430 $\pm$ 523 (4)	
19.5	30 min	2450 $\pm$ 423 (4)	
19.5	60 min	1300 $\pm$ 236 (4)	21100 $\pm$ 1460 (16)
20.5	1 day	60 $\pm$ 6 (2)	716 $\pm$ 43 (10)
21.5	2 days		246 $\pm$ 7 (39)
22.5	3 days		145 $\pm$ 10 (17)
23.5	4 days		104 $\pm$ 9 (16)

¹ Mean $\pm$ S.E.

² Numbers in parentheses, number of observations.

suggests that no degradation of fetal liver glycogen occurs in this period. When gestation is prolonged for two days, the value obtained for cpm ^3H present in total liver glycogen is decreased by 68%, and the total glycogen content of the liver is decreased by similar factor (64%).

IN VIVO GLUCONEOGENESIS FROM LABELED LACTATE

Conversion of [^{14}C]Lactate to Glucose in Control Fetuses Given Injections of Saline and in the Mothers. Table 3 shows the percentage of ^{14}C as glucose in the blood of control fetuses and in the mothers after 30 min of incorporation. The values in the control fetuses are always lower than the values in the corresponding mothers at the same time and so are consistent with a maternal origin for the fetal glucose. There is no significant difference in the conversion of lactate to glucose between the term fetuses and the postmature fetuses or between the term mothers and the prolonged mothers.

Conversion of [^{14}C]Lactate to Glucose in Fetuses Given Injections Directly with [^{14}C]Lactate. Results from Table 4 show that in the term fetuses the percentage of radioactivity as glucose is very low. This is explained by the high quantity of [^{14}C]lactate not converted. When the radioactivity of maternal origin is subtracted, the percentage of ^{14}C as glucose is less than 2%. Therefore, gluconeogenesis is negligible in the term fetuses. It is the same in the postmature fetuses because in the fetuses directly given injections with [^{14}C]lactate, the percentage of ^{14}C as glucose is also very low.

DEVELOPMENT OF GLUCONEOGENESIS IN THE POSTMATURE NEWBORN

Blood Glucose Levels during the First 12 Postnatal Hr Fasted Newborns. Thirty min after birth, the same blood glucose level is observed in term and postmature neonates (Fig. 1). Hypoglycemia observed in term newborns by 3 hr postpartum (p.p.) is transitory, and at six hr, blood glucose returns to normal. In contrast,

Table 2. Time course of incorporation of [^3H]glucose into fetal liver glycogen after injection of D-[^3H]glucose to fetuses on day 19.5 p.c.

Day p.c.	Time after injection	cpm ^3H /100 mg glycogen	cpm ^3H in total liver glycogen
19.5	60 min	36000 $\pm$ 5480 ¹ (16) ²	870 $\pm$ 135 (16)
20.5	1 day	22400 $\pm$ 2350 (9)	2470 $\pm$ 313 (9)
21.5	2 days	10400 $\pm$ 794 (39)	2720 $\pm$ 145 (39)
22.5	3 days	9100 $\pm$ 547 (17)	1350 $\pm$ 102 (17)
23.5	4 days	10900 $\pm$ 1250 (16)	1000 $\pm$ 116 (16)

¹ Mean $\pm$ S.E.

² Numbers in parentheses, number of observations.

Table 3. Percentage of ^{14}C as glucose in the blood of control fetuses and in maternal blood after injection of [^{14}C]lactate; control fetuses were given an injection of saline, and labeled lactate was injected into other fetuses of the same litter

Day p.c.	Time after injection (min)	Mothers	Control fetuses
21.5			
	5	15 $\pm$ 3 ¹ (8) ²	
	15	24 $\pm$ 4 (7)	
	30	33 $\pm$ 3 (9)	25 $\pm$ 6 (8)
23.5			
	5	12 $\pm$ 4 (5)	
	15	25 $\pm$ 3 (7)	
	30	28 $\pm$ 5 (6)	22 $\pm$ 4 (10)

¹ Mean $\pm$ S.E.

² Numbers in parentheses, number of observations.

Table 4. Percentage of ^{14}C as glucose in fetuses given injections of [^{14}C]lactate

Day p.c.	Noncorrected values	Corrected values ¹
21.5	2.5 $\pm$ 0.6 ² (8) ³	1.7 $\pm$ 0.4 (8)
23.5	2.4 $\pm$ 1.0 (10)	1.0 $\pm$ 0.4 (10)

¹ Correction for labeling of maternal origin is given by the values obtained in the control fetuses given injections of saline only.

² Mean $\pm$ S.E.

³ Numbers in parentheses, number of observations.

BLOOD GLUCOSE

Fig. 1. Blood glucose levels in postmature newborns. Postmature (Δ) or term ($\bullet$) newborns were delivered by caesarean section on day 23.5 and 21.5 p.c., respectively, and maintained fasted at normal body temperature for 6 hr. In other experiments, postmature ($\triangle$) or term ($\circ$) newborns were given to a foster mother at birth and allowed to suckle for 6 or 12 hr. Mean $\pm$ S.E.

hypoglycemia aggravates in postmature newborns, and by 6 hr p.p., blood glucose is only 22 ± 4 mg/100 ml. These results confirm our previous observations (25).

Fed Newborns. Suckling is without effect on the 6 hr p.p. blood glucose level in term newborn. In fed postmature newborns, hypoglycemia does not develop, and by 12 hr p.p., blood glucose level is not significantly different of the value observed in term newborns (Fig. 1).

Hepatic Enzyme Activities in the Postmature Newborn. Glucose-6-phosphatase activity is low at birth in term animals and is increased 2.7-fold 6 hr p.p. In the postmature animals, the enzyme activity is always increased when compared to the value obtained in term animals (Table 5). PEPCK activity is very low at birth and 1 hr p.p. in the term neonate; it increases 44-fold by 6 hr p.p. In the postmatures, PEPCK activity is increased 23-fold at birth by comparison to the term neonates, and between 0 and 6 hr p.p., this activity increases by 2.8-fold (Table 5).

In Vivo Gluconeogenesis from Labeled Lactate in Postmature Newborns. Results are presented in Table 6. In fasted newborns, the percentage of injected [^{14}C]lactate converted to glucose is very low 30 min after birth in both term and postmature animals. By 3 hr p.p., the percentage of conversion and the rate of gluconeogenesis are increased, respectively, by 7.5- and 23-fold in the postmatures as compared to the term animals. By 6 hr p.p., the percentage of conversion is similar in the 2 groups whereas the rate of gluconeogenesis is significantly lower in the postmature group. In fed term newborns at 6 hr, the percentage of conversion of lactate and the rate of gluconeogenesis is the same as in the fasted group. In contrast, the fed postmature neonates exhibit an

Table 5. Liver enzyme activities in term and postmature neonates

		Hr after birth			
		0	1	3	6
Glucose-6-phosphatase ($\mu\text{M Pi/min/g protein}$)	TN ¹	21.1 $\pm$ 2.7 ² (6) ³	22.3 $\pm$ 1.1 (6)	29.9 $\pm$ 1.9 (6)	56.1 $\pm$ 2.7 (6)
	PN	46.2 $\pm$ 2.7 ³ (6)	59.5 $\pm$ 3 ⁴ (6)	58 $\pm$ 5 ⁴ (4)	74.5 $\pm$ 4.4 ⁵ (6)
PEPCK ($\mu\text{M CO}_2\text{/min/g protein}$)	TN	0.5 $\pm$ 0.1 (6)	1.1 $\pm$ 0.1 (8)	8.3 $\pm$ 1.2 (8)	22.2 $\pm$ 0.6 (8)
	PN	11.5 $\pm$ 0.7 ⁴ (5)	14 $\pm$ 1.1 ⁴ (4)	27.1 $\pm$ 1.9 ⁴ (7)	32.4 $\pm$ 2.1 ⁴ (8)

¹ TN, term neonates. PN, postmature neonates.² Mean $\pm$ S.E.³ Numbers in parentheses, number of observations.⁴ $P < 0.001$ when compared with corresponding value in the term neonates.⁵ $P < 0.01$ when compared with corresponding value in the term neonates.

increased gluconeogenesis when compared to the fasted group. In these fed postmature neonates, the gluconeogenic activity is the same as in term neonates 2 days after birth, *i.e.*, of the same conceptual age.

DISCUSSION

GLUCOSE METABOLISM IN THE POSTMATURE FETUS

In the postmature fetus, liver glucose-6-phosphatase and PEPCK activities were increased when compared to the term fetus (23), and we have suggested that this process is explained by low insulin/glucagon ratio in the plasma (24). Therefore, the relationship between the induction of these enzyme activities and the incorporation *in vivo* of ¹⁴C from lactate into glucose was determined during fetal life. Our data which are obtained in mothers under pentobarbital anesthesia for the complete experiment, are consistent with fetal gluconeogenesis being inactive in the postmature fetus as well as in the normal-term fetus. In the postmature fetus the percentage of conversion of lactate to glucose is as low as in the term fetus, and the lactate pool is only slightly increased (the plasma lactate concentration is the same and the body weight increment is about 20%). Fetal gluconeogenesis from lactate could be undetectable if the transfer of [¹⁴C]glucose from the fetus to the mother was much faster than the transfer of [¹⁴C]lactate. However, we have checked by simultaneous injection of [¹⁴C]lactate plus [6-³H]glucose to the fetus that the transfer of glucose to the mother proceeds exactly at the same rate that the transfer of lactate.

As a consequence, it appears that elevated PEPCK activity in fetal liver is not the only initiating factor necessary to obtain a functional gluconeogenic pathway, although the key role of PEPCK has been previously emphasized by some authors (2, 10, 35). However, all their observations were obtained *in vitro* in unphysiologic conditions. The only *in vivo* data in the nonruminant monogastric fetus are those of Philippidis and Ballard (22). They found that despite increased PEPCK activity due to glucagon administration, *in vivo* fetal gluconeogenesis is not occurring. They attributed this to hypoxia due to anesthesia of the mother because they obtained a substantial *in vivo* incorporation of [¹⁴C]pyruvate into [¹⁴C]glucose only when anesthesia was administered for minimal times. However, in the experiments of Philippidis and Ballard, the participation of maternal gluconeogenesis in the amount of labeled glucose found in the fetus has not been determined and is probably a source of error. Moreover, these authors have not demonstrated that slight anesthesia ameliorates fetal PO₂. In experiments not shown here, we have corrected the maternal PO₂ by oxygen administration to the mother under pentobarbital anesthesia (78 $\pm$ 5 mm Hg under pentobarbital, 116 $\pm$ 7 mm Hg under pentobarbital plus 30 min oxygenation, and 103 $\pm$ 2 mm Hg without anesthesia). In the fetuses of these oxygenated mothers, fetal PO₂ was slightly increased, but the difference was not significant (9 $\pm$ 1 mm Hg under anesthesia of the mother and 12 $\pm$ 2 mm Hg under anesthesia plus 30 min oxygenation of the

mother). It is not possible to consider the fetal PO₂ value presently obtained as the PO₂ value of the term fetus *in vivo* because one cannot determine PO₂ in fetus of unanesthetized mother.

Another prerequisite to obtain active pathway is nonlimiting concentrations of substrates; in our experiments the plasma lactate level is more elevated in the fetus than in the newborn in both postmature and term animals. This eliminates fetal lactate as rate-limiting step in the fetal gluconeogenic pathway. The decreased hepatic glycogen content together with the decrease by the same percentage of the ³H radioactivity present in the total hepatic glycogen clearly demonstrate that degradation of glycogen occurs in the postmatures. Previous data (24) indicate that the fetal hormonal response, *i.e.*, insulin fall and glucagon rise, is appropriate to fetal hepatic glycogenolysis. One may calculate the fetal glucose production resulting from this hepatic glycogenolysis in the postmature fetus; it is about 2 g/day/kg body weight. The turnover of glucose is not known in the fetal rat, but if one takes into account the value obtained in the newborn rat according to Girard and Guillet (12), *i.e.*, 18 g/day/kg body weight, it would seem that transplacental transport of maternal glucose remains the major source of fetal glucose during postmaturity. It is also noteworthy that glycogen synthesis is inhibited during postmaturity, and this may be related to the low plasma insulin (24) and to the fact that corticosteronemia is lower after 21.5 days p.c. than before (28). Besides, our radioisotopic experiments in the normal fetuses confirm that glycogen synthesis is active from day 19.5 p.c. onward and indicate that there is normally no glycogen degradation in the period under study. This conclusion is similar to that of Devos and Hers (8) who claimed that there was no turnover of glycogen in the fetal liver of the rat. It does not agree with the results of Watts and Gain (34) and of Gilbert and Bourbon (9) who assumed that there is a continual turnover of liver glycogen. However, in our experiments, the radioactive glucose incorporated into glycogen on day 19.5 p.c. could have been covered later by unlabeled units on the periphery of the molecule, and if only peripheral units participate in the turnover, the degradation of these unlabeled units would not be noticed. Nevertheless, Devos and Hers in similar experiments have shown that a large proportion of the radioactivity incorporated on day 19.5 p.c. was still present 38 hr later on the outer chains of glycogen. The general conclusions that can be drawn from this study of carbohydrate metabolism in the postmature fetus are: no functioning of gluconeogenic pathway, inhibition of liver glycogen synthesis, and stimulation of liver glycogenolysis. Moreover, inasmuch as fetal glycogen synthesis is inhibited, it is inferred that the quantity of maternal glucose transferred across the placenta may be considered as reduced (27, 33) but nevertheless is appropriate to maintain normal blood glucose level in the postmature fetus.

GLUCOSE METABOLISM IN THE POSTMATURE NEONATE

The study focused upon the early period of postnatal life, a period characterized by the pronounced and irreversible hypogly-

Table 6. *In vivo* gluconeogenesis from [¹⁴C]lactate in term and postmature neonates

	Hr after birth									
	0.5		3		6		12		48 (TN)	
	TN	PN	TN	PN	TN	PN	TN	PN	TN	PN
Fasted										
Lactate pool	16 ± 1 ¹ (8) ²	25 ± 1 (4)								
Percentage of conversion in 30 min	0.2 ± 0.05 (14)	0.5 ± 0.2 (18)	5 ± 0.3 (8)	18 ± 7 (16)	6 ± 1 (12)	4.4 ± 0.6 (6)				
Gluconeogenic rate	0.6 ± 0.2 (14)	1.9 ± 0.7 (18)	1.1 ± 0.1 (6)	8.3 ± 0.6 (7)	6.9 ± 1 (10)	6.5 ± 0.7 (8)				
			1.0 ± 0.1 (6)	23 ± 2 (7)	8.2 ± 1.2 (10)	4.5 ± 0.5 (8)				
Fed										
Lactate pool					5 ± 0.5 (9)	8 ± 1 (5)	4.5 ± 0.4 (8)	4.4 ± 0.6 (4)	6.6 ± 0.4 (10)	
Percentage of conversion in 30 min					6.1 ± 0.5 (14)	8 ± 1 (9)	7 ± 0.3 (13)	12.4 ± 0.6 (9)	11 ± 1 (10)	
Gluconeogenic rate					6.4 ± 0.6 (14)	10 ± 1 (9)	6.2 ± 0.3 (13)	9 ± 0.4 (9)	12 ± 1 (10)	

¹ Mean ± S.E.² Numbers in parentheses, number of observations.

cemia experienced by the postmature newborn when maintained fasted (25).

During the first hr after delivery, our *in vivo* data about conversion of labeled lactate to glucose show that the gluconeogenic pathway is not functioning in spite of a very high PEPCK activity in the postmatures. This clearly indicates that immediately after birth there is a rate-limiting factor for glucose synthesis other than lack of enzymic activity. Liver hypoxia has been proposed as this rate-limiting factor (21). Besides, no significant amounts of glycogen are mobilized during this period. As a consequence, blood glucose level decreases (25). During the next period, from 1 to 6 hr after birth, striking differences are reported. In the normal-term neonates, the activation of hepatic enzymes critical for glucose production takes place as demonstrated previously (2, 3, 7, 10, 35). Equivalent changes are shown in the postmatures, but activities are always higher than in the normals. The concurrent fall in insulin level and in insulin/glucagon molar ratio (24) probably contributed to the changes observed. By 3 hr p.p., the percentage of conversion and the rate of gluconeogenesis from lactate are very elevated in the postmatures as compared to the term neonates. By 6 hr p.p., gluconeogenesis in the postmatures becomes very weak although the percentage of conversion is maintained. Limitations of substrate availability as suggested by the drop of plasma lactate level probably explain this discrepancy. Concerning postnatal hepatic glycogenolysis, we have previously shown (25) that it operates normally in the postmature animal, but the reduced glycogen stores are exhausted by 6 hr p.p., a time characterized by the development of profound hypoglycemia. This implies that glycogenolysis is at first a more important metabolic process than is gluconeogenesis to satisfy the glucose requirement of the fasted neonate.

Major differences exist between the fed and the fasted postmature neonates. By 6 and 12 hr p.p., fed postmature neonates exhibit normal blood glucose levels. The rate of gluconeogenesis is higher than in the fasted animals. Hence, as suckling is established, the organism is able to sustain glycemia by gluconeogenesis, owing to the new source of exogenous gluconeogenic substrates largely in the form of aminoacids and glycerol. Observations in normal newborns (13) indicate that in animals fasted 16 hr, both energetic and gluconeogenic substrates are lacking. In contrast, in the postmatures fasted 6 hr, it may be observed that the energetic substrate supply is not yet a rate-limiting step because the percentage of conversion is maintained.

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