Postnatal hypoglycaemia and gluconeogenesis in the newborn rat

Delayed onset of gluconeogenesis in prematurely delivered newborns

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1. The concentrations of glucose and lactate in the blood and of liver glycogen, and the phosphoenolpyruvate carboxykinase activity in liver and kidney of term and preterm newborn rats, were studied during the first 6 h *post partum*. Rates of lactate turnover and gluconeogenesis *in vivo* from [U-¹⁴C]lactate at 3 h and 6 h *post partum* were also quantified. 2. The development of the prolonged postnatal hypoglycaemia observed after birth in the premature newborn rat is associated with lower rates of glucose production through glycogenolysis and gluconeogenesis; liver glycogenolysis was the main contributing factor to the glucose available during the neonatal period studied in both groups. 3. Delayed induction of liver phosphoenolpyruvate carboxykinase activity was observed in premature newborn rats. Renal phosphoenolpyruvate carboxykinase activity increased 72% from birth in preterm newborns, but only a 25% increase was found in term newborns during the same experimental period. 4. The gluconeogenesis *in vivo* from [U-¹⁴C]lactate paralleled the appearance of cytosolic phosphoenolpyruvate carboxykinase activity in the liver of both groups of newborns. 5. Blood lactate concentrations remained higher in preterm than in term newborns. The postnatal utilization of lactate via the gluconeogenic pathway in either group of newborns was always less than 20% of the total lactate used. 6. The results presented are discussed in relation to the development of postnatal hypoglycaemia and gluconeogenesis in the premature newborn rat.

Immediately after birth, the newborn rat has to utilize its own energy reserves until suckling begins and adaptation to a high-fat diet is established (Snell & Walker, 1973; Girard *et al.*, 1973; Cuezva *et al.*, 1980; Medina *et al.*, 1980). It is generally known that during the first postnatal hour the full-term newborn rat develops a profound hypoglycaemia (Girard *et al.*, 1973; Di Marco *et al.*, 1976; Cuezva *et al.*, 1980), which is likely to be a consequence of the high rates of glucose utilization (Vernon & Walker, 1972; Snell & Walker, 1973) together with low rates of glucose production by glycogenolysis and gluconeogenesis (Cake *et al.*, 1971; Snell & Walker, 1973; Pearce *et al.*, 1974). Nevertheless,

full-term newborns reach normoglycaemia within the first 3 h *post partum* (Girard *et al.*, 1973; Di Marco *et al.*, 1976; Cuezva *et al.*, 1982a), because, during the second hour, an increase in the rates of glucose production and an abrupt decrease in those of glucose utilization occur (Snell & Walker, 1973).

It has been reported that preterm newborns developed a profound hypoglycaemia in the postnatal period (Di Marco *et al.*, 1976; Cuezva *et al.*, 1980) and that they recovered from it 2–3 h later than full-term newborns (Di Marco *et al.*, 1976). Since premature newborn infants are particularly vulnerable to hypoglycaemia (Lubchenco & Bard, 1971; Gutberlet & Cornblath, 1976), which in turn is associated with neurological dysfunction (Beard *et al.*, 1971), the aims of the present research were to

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establish the factors involved in the development of hypoglycaemia in preterm newborn rats and to quantify the contribution of the gluconeogenic pathway to the glucose available during the first 6 h *post partum*.

Experimental

Materials

Chemicals. L-[U- 14 C]Lactate and NaH 14 CO $_3$ were obtained from The Radiochemical Centre, Amersham, Bucks., U.K. Analytical-grade anion-exchange resin Dowex AG1-X8 (Cl $^-$ form; 200–400 mesh) was purchased from Bio-Rad Laboratories, Richmond, CA, U.S.A. Other chemicals were from Sigma Chemical Co., St. Louis, MO, U.S.A., and Merck, Darmstadt, Germany.

Animals. Timed-pregnant rats weighing 200 g were fed on standard laboratory chow and water *ad libitum*. Females were caged overnight with males and conception was assumed next morning by the presence of spermatozoa in the vagina. Pregnancy was confirmed at day 19 of gestation. The foetuses were delivered by rapid hysterectomy from cervically dislocated pregnant rats on days 20.5 and 21.5 of gestation. Newborns were considered preterm, weighing 4.1 ± 0.1 g (mean $\pm$ S.E.M.), or term, weighing 5.2 ± 0.1 g for 20.5 and 21.5 days respectively. The newborns were maintained without feeding as previously described (Cuezva *et al.*, 1980).

Methods

Blood and liver sampling. Newborn rats were killed by decapitation; 100 μ l of blood was collected in disposable pipettes and quickly transferred to 0.5 ml of 0.06 M-NaOH for deproteinization. Neutralization was performed by adding 0.5 ml of 1% (w/v) ZnSO $_4$. The protein precipitated was removed by centrifugation (5 min at 15 600 g). The livers used to measure glycogen concentrations were freeze-clamped in liquid N $_2$ (Wollenberger *et al.*, 1960).

Measurement of metabolites and enzyme activities. Glucose and lactate concentrations in blood, or in the chromatographic fractions, were measured by the methods of Bergmeyer *et al.* (1974) and Gutmann & Wahlefeld (1974) respectively. Glycogen concentrations were assayed as described by Keppler & Decker (1974). Liver and kidney phosphoenolpyruvate carboxykinase activities were measured in liver and kidney cytosols by the method described by Ballard & Hanson (1967). One unit of activity represents 1 μ mol of H 14 CO $_3$ fixed/min at 37°C.

Studies in vivo. Term and preterm newborns were intraperitoneally injected with 20 μ l of 0.9% (w/v) NaCl containing 2 μ Ci of L-[U- 14 C]lactate by using

a 25 μ l Hamilton syringe equipped with a $\frac{1}{8}$ -mm-gauge needle (Hamilton Co., Reno, NV, U.S.A.). At the time intervals shown in Figs. 1 and 2, newborns were decapitated and 100 μ l samples of blood collected as described above. Blood glucose and lactate were separated with Pasteur pipettes filled with anion-exchange resin Dowex AG1-X8 (Cl $^-$ form); 0.5 ml fractions were collected. Glucose (98%) and lactate (99%) were recovered in the eluate fractions 2 and 13 respectively, by the method previously described (Cuezva *et al.*, 1982b). The radioactivity of [14 C]glucose and L-[U- 14 C]-lactate was measured by liquid-scintillation counting [dioxan/toluene/ethanol (1:1:1, by vol.) containing 1,4-bis-(4-methyl-5-phenyloxazol-2-yl)benzene (0.5 g/l) and 2,5-diphenyloxazole (5 g/l)]. The background and respective counting efficiencies were taken into consideration in the correction of the c.p.m. found in each sample. The specific radioactivities were expressed as d.p.m./ μ mol of substrate.

Calculations and analysis of the data. In the experiments *in vivo*, the blood glucose and lactate concentrations were maintained fairly constant throughout the course of the experiment. Under these conditions, i.e. in the steady state, the rates of glucose or lactate released into the circulating blood should equal the rate of removal of the metabolite from the circulation (Girard & Guillet, 1975) and will be referred to as the turnover rates of the metabolite (R , μ mol/min per 100 g body wt.). A plot of the log of specific radioactivity of blood lactate versus time was constructed, and is represented by the exponential equation $S = S_0 e^{-kt}$ (Okajima & Ui, 1979), where S is the specific radioactivity (d.p.m./ μ mol) of the metabolite in the blood sample at time t (S_0 is the value at zero time) and k is the first-order rate constant or the fractional turnover rate (min^{-1}). The lactate turnover rate, R , was calculated by the analysis of Okajima & Ui (1979). The method for calculation of the lactate-turnover rate described above assumes that the lactate newly synthesized and released into circulation is not labelled with radioisotopes, a reliable assumption because of the shortness of the experimental period and the low specific radioactivity of the blood glucose attained compared with the labelled precursor (see Figs. 1 and 2). Since the rates of incorporation of [14 C]-lactate into blood glucose were linear during the experimental periods studied (see Figs. 1 and 2), the rates of gluconeogenesis were calculated from the mean specific radioactivities of blood lactate (Cuezva *et al.*, 1982b) at each experimental period studied. Glucose space was considered to be 80% of the body weight, according to previous calculations (Cuezva & Patel, 1980a). Statistical analysis was performed by Student's t test. Statistical linear-regression correlation was applied to the linear plots

with the aid of a digital computer using a FORTRAN IV language. *P* values of 0.05 or less were taken as significant, and the results were expressed as the means $\pm$ S.E.M.

Results

Postnatal changes in liver glycogen, blood glucose and lactate concentrations

Table 1 shows the postnatal changes in liver glycogen, blood glucose and lactate concentrations during the first 6 h *post partum* in term and preterm newborn rats. At the time of delivery, liver glycogen concentrations of preterm foetuses were 25% lower ($P < 0.01$) than those observed in term foetuses. Glycogenolysis was induced soon after birth in both groups of newborns. By 3 h *post partum*, no differences were observed in the concentrations of liver glycogen between the two groups of newborns studied. At birth, blood glucose concentrations were higher ($P < 0.025$) in term than in preterm foetuses. During the first postnatal hour, both groups of newborns developed a profound hypoglycaemia, but term newborns reached normoglycaemia by 3 h *post partum*, in contrast with preterm newborns, whose blood glucose concentrations remained very low. During the next 3 h, a significant increase in blood glucose concentration was observed in preterm newborns, with the concentration of blood glucose at 6 h after birth in term newborns being lower than in premature newborn rats. Blood lactate concentrations increased in preterm newborns during the first postnatal hour, but no changes were observed in term newborns during the same experimental period. After the first hour of extrauterine life, blood lactate concentrations decreased in both groups of newborns, following similar patterns. However, the concentrations of blood lactate were significantly higher in preterm newborns than in term newborn rats at all the time points studied.

Rates of lactate turnover and gluconeogenesis in vivo

Figs. 1 and 2 show the logarithm of the specific radioactivity of blood lactate and the specific radioactivity itself of blood glucose after the intra-peritoneal injection of 2 μ Ci of L-[U- 14 C]lactate to term and preterm newborns at 3 h and 6 h *post partum*, respectively, and during the first 15 min after the injection. The radioactive lactate was administered when blood lactate and glucose concentrations were in steady state (see the upper panel of each Figure). At the 3 h *post partum* (Fig. 1), the plot of the log of specific radioactivity of blood lactate versus time showed slopes, *m*, of -0.024 min^{-1} ($r = 0.9938$; $P < 0.001$) for term newborns and -0.034 min^{-1} ($r = 0.9949$; $P < 0.001$) for preterm newborns. The slopes for the plot of specific radioactivity of blood glucose versus time at 3 h *post partum* were 1309 d.p.m. $\cdot \mu\text{mol}^{-1} \cdot \text{min}^{-1}$ ($r = 0.9957$; $P < 0.001$) and 2295 d.p.m. $\cdot \mu\text{mol}^{-1} \cdot \text{min}^{-1}$ ($r = 0.9801$; $P < 0.01$) for term and preterm newborns respectively. At 6 h *post partum* (Fig. 2), the plot of the log of specific radioactivity of blood lactate versus time showed slopes, *m*, of -0.0355 min^{-1} ($r = 0.9992$; $P < 0.001$) and -0.0180 min^{-1} ($r = 0.9981$; $P < 0.001$) for term and preterm newborns respectively. The slopes for the plot of the specific radioactivity of blood glucose versus time at 6 h *post partum* were 1812 d.p.m. $\cdot \mu\text{mol}^{-1} \cdot \text{min}^{-1}$ ($r = 0.9995$; $P < 0.001$) for term newborns and 2459 d.p.m. $\cdot \mu\text{mol}^{-1} \cdot \text{min}^{-1}$ ($r = 0.9997$; $P < 0.001$) for preterm newborns.

By using the results depicted in Figs. 1 and 2, the turnover rate of blood lactate and the rate of lactate incorporation into blood glucose were calculated (Table 2). At 3 h *post partum*, no significant differences were observed in the turnover rate of blood lactate between term and preterm newborns. At 6 h *post partum*, term newborns showed an increase in the turnover rate of blood lactate

Table 1. *Postnatal changes in liver glycogen, blood glucose and blood lactate concentrations in term and preterm newborn rats during the first 6 h of extrauterine life*

Term and preterm newborn rats were delivered from pregnant rats on days 20.5 and 21.5 of gestation respectively. The newborns were maintained in a Humidicrib at 37°C without feeding and were exsanguinated at the times depicted in the Table. The results are the means $\pm$ S.E.M. for eight to ten newborns from four or five different mothers. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.0005$ for comparison of term and preterm newborns at the same time periods.

Newborn	Foetal weight (g)	Time after birth (h)	Hepatic glycogen ($\mu\text{mol/g}$ wet wt.)	Blood glucose (mM)	Blood lactate (mM)
Term	5.23 ± 0.10	0	433 ± 35	3.40 ± 0.37	7.56 ± 0.37
		1	398 ± 39	1.77 ± 0.12	7.37 ± 0.62
		3	232 ± 12	4.58 ± 0.38	2.59 ± 0.32
		6	135 ± 8	2.92 ± 0.11	1.93 ± 0.21
Preterm	4.07 ± 0.10	0	$310 \pm 23^{**}$	$2.30 \pm 0.21^*$	7.03 ± 0.61
		1	$300 \pm 11^*$	1.66 ± 0.13	$10.43 \pm 0.57^{**}$
		3	222 ± 16	$1.39 \pm 0.13^{***}$	$4.81 \pm 0.73^{***}$
		6	107 ± 7	3.21 ± 0.21	1.83 ± 0.22

Fig. 1. Logarithm of the specific radioactivity of $[^{14}\text{C}]$ lactate, the specific radioactivity of $[^{14}\text{C}]$ glucose, and lactate and glucose concentrations in blood 20 min after the injection of $[U-^{14}\text{C}]$ lactate in term (●) and preterm (▲) newborns at 3 h post partum

The newborns were maintained at 37°C in a Humidicrib without feeding. Term and preterm newborns were intraperitoneally injected with 2 μCi of L- $[U-^{14}\text{C}]$ lactate at 3 h post partum. They were decapitated at 5, 10, 15 or 20 min after the injection and 100 μl samples of blood were collected. Blood glucose and lactate were separated as described under 'Methods', and the specific radioactivity of each metabolite is represented as d.p.m./ μmol . The results shown at each point are means $\pm$ S.E.M. for four to five newborns from four or five different mothers.

Table 2. Rates of lactate turnover and of $[U-^{14}\text{C}]$ lactate incorporation into blood glucose in term and preterm newborn rats at 3 h and 6 h post partum

Term and preterm newborn rats were intraperitoneally injected with 2 μCi of L- $[U-^{14}\text{C}]$ lactate at 3 h or 6 h post partum, and were exsanguinated at 5, 10, 15 or 20 min after the injection. The results shown in this Table have been obtained from the experimental values of Figs. 1 and 2, and are means $\pm$ S.E.M. * $P < 0.025$, ** $P < 0.0025$, *** $P < 0.0005$, for comparison of term and preterm newborns by Student's t test.

Time post partum ...	3 h		6 h	
Parameter	Term newborns	Preterm newborns	Term newborns	Preterm newborns
Lactate fractional turnover rate, k (min^{-1})	0.0555 ± 0.0003	$0.0774 \pm 0.0007^{***}$	0.0817 ± 0.0027	$0.0414 \pm 0.0011^{***}$
Lactate turnover rate, R ($\mu\text{mol}/\text{min}$ per 100 g body wt.)	38.06 ± 1.96	42.72 ± 2.90	74.26 ± 8.22	$48.18 \pm 2.60^*$
Rate of $[^{14}\text{C}]$ lactate incorporation into blood glucose ($\mu\text{mol}/\text{min}$ per 100 g body wt.)	6.52 ± 0.46	$2.95 \pm 0.07^{***}$	11.00 ± 0.25	$9.45 \pm 0.03^{**}$
Percentage of R incorporated into blood glucose	17.34 ± 2.08	$7.00 \pm 0.61^{**}$	15.10 ± 1.32	18.23 ± 1.80

Fig. 2. Logarithm of the specific radioactivity of [¹⁴C]lactate, the specific radioactivity of [¹⁴C]glucose, and lactate and glucose concentrations in blood 15 min after the injection of [¹⁴C]lactate in term (●) and preterm (▲) newborns at 6 h post partum
For experimental details see the legend to Fig. 1.

Table 3. Phosphoenolpyruvate carboxykinase activity in liver and kidney of term and preterm newborn rats during the first 6 h post partum

Term and preterm foetuses were delivered from pregnant rats on days 20.5 and 21.5 of gestation respectively. At 0, 3 h and 6 h post partum, the newborns were exsanguinated and their livers and kidneys removed to determine the activity of phosphoenolpyruvate carboxykinase. One unit of activity represents 1 μmol of H¹⁴CO₃ fixed/min at 37°C. The results are means ± s.e.m. for the numbers of rats shown in parentheses. **P* < 0.005 and ***P* < 0.0005 for comparison of preterm and term newborns by Student's *t* test.

		Phosphoenolpyruvate carboxykinase (units/g of tissue)			
		Liver		Kidney	
Time post partum (h)	Newborns ...	Term	Preterm	Term	Preterm
0		0.015 ± 0.002 (6)	0.015 ± 0.002 (6)	0.39 ± 0.03 (8)	0.18 ± 0.02 (8)**
3		0.240 ± 0.016 (8)	0.120 ± 0.011 (8)**	0.38 ± 0.02 (8)	0.22 ± 0.01 (8)**
6		0.680 ± 0.087 (8)	0.400 ± 0.066 (8)*	0.49 ± 0.05 (6)	0.31 ± 0.07 (8)*

(*P* < 0.0005) compared with the same group of newborns at 3 h post partum. In contrast, preterm newborns showed no differences in the lactate turnover rate between 3 and 6 h post partum. Consequently, significant differences (*P* < 0.025) in the lactate turnover rate between term and preterm

newborns at 6 h post partum were observed. The rates of gluconeogenesis *in vivo* from radioactive lactate were significantly lower in preterm newborns as compared with term newborns at 3 h and 6 h post partum (Table 2). The rates of gluconeogenesis were increased 2–3-fold between the 3 h and 6 h post

partum in both groups of newborn rats. Term newborns incorporated into glucose about 17% of the lactate turned over at 3 h *post partum*, whereas preterm newborns reached this value 3 h later.

Phosphoenolpyruvate carboxykinase activity

Hepatic cytosolic phosphoenolpyruvate carboxykinase activity (Table 3) was similar in both groups of newborns at birth. At 3 h *post partum*, term newborns showed twice the activity found in preterm liver ($P < 0.0005$). At 6 h after birth, phosphoenolpyruvate carboxykinase activity was still higher in the liver of term rats than in that of premature rats ($P < 0.005$). Kidney phosphoenolpyruvate carboxykinase activity (Table 3) was higher (2-fold) in term foetuses than in premature foetuses at birth. Kidney phosphoenolpyruvate carboxykinase activity increased in both groups of newborns during the observation period, but after 6 h of extrauterine life enzyme activities were still higher in term newborns.

Discussion

Blood glucose concentration falls rapidly in preterm and term newborn rats after birth (Table 1; see also Di Marco *et al.*, 1976; Cuezva *et al.*, 1980), probably as a consequence of the rapid utilization of glucose by the neonatal tissues (Cake *et al.*, 1971; Girard & Guillet, 1975), together with a transient inability of the newborn liver to supply sufficient glucose, through glycogenolysis (Table 1; Snell & Walker, 1973; Girard *et al.*, 1973) and/or gluconeogenesis (Table 2; Yeung & Oliver, 1967; Ballard, 1971; Pearce *et al.*, 1974). In the present paper, the results reported above will be discussed with regard to the rates of glucose formation by glycogenolysis and gluconeogenesis.

It has been assumed that in neonatal liver glycogenolysis is stimulated by the increase in plasma catecholamine concentrations (Pollak, 1977) secreted after delivery (Cuezva *et al.*, 1982a) as a result of the development of postnatal hypoglycaemia (Cuezva & Patel, 1982). Other factors involved are the decrease observed in the insulin/glucagon ratio after birth (Girard *et al.*, 1973; Di Marco *et al.*, 1978; Cuezva *et al.*, 1982a) and the stimulatory effect of hypoglycaemia on glycogenolysis (Pines *et al.*, 1976; Bashan *et al.*, 1979; Martin *et al.*, 1981). Some of these mechanisms could be related to a cyclic AMP-dependent process, since it has been shown that, in newborns of normal, mildly and severely hyperglycaemic rats, liver glycogenolysis was induced after the postnatal increase in liver cyclic AMP (Cuezva & Patel, 1980b; Cuezva *et al.*, 1982a). Similarly, the development of gluconeogenesis is a cyclic AMP-dependent process (Hanson *et al.*, 1975).

The acute postnatal hypoglycaemia observed in preterm newborns at 3 h *post partum* (Table 1) may be the result of lower rates of glycogenolysis (26 and 16 $\mu\text{mol/min}$ per 100 g body wt. for term and preterm newborns respectively) and of gluconeogenesis (Table 2). The present observation is consistent with the delayed increase in hepatic cyclic AMP concentrations observed in the premature newborn rat (Di Marco & Oliver, 1978) as a result of the higher insulin/glucagon molar ratios observed in this group of newborns during the first postnatal hours (Di Marco *et al.*, 1978). The delayed increase in the hepatic cyclic AMP concentration in the premature newborn rat may be also related to the delayed appearance of phosphoenolpyruvate carboxykinase activity in the liver (Table 3), and so to the lower rates of gluconeogenesis observed in this group of newborns (Table 2). However, it is worth noting that the main factor contributing to the development of hypoglycaemia in the premature newborn rat is the lower rates of glycogenolysis, since the glucose supplied by gluconeogenesis at 3 h *post partum* only accounts for 12% and 9% of that from glycogenolysis in term and preterm newborns, respectively. Although hepatic and renal phosphoenolpyruvate carboxykinase activity increased in term newborns between 3 and 6 h *post partum* (Table 3), and a concurrent increase in the gluconeogenesis *in vivo* was observed (Table 2), the blood glucose concentration fell during this period (Table 1). This fall in the blood glucose concentration may be due to the sharp decrease observed in the rates of glycogenolysis (26 and 10 $\mu\text{mol/min}$ per 100 g body wt. at 3 and 6 h respectively). The abrupt change that term newborns show in rates of glycogenolysis could be explained by the partial inhibitory effect of glucose on liver glycogenolysis (Stalmans *et al.*, 1974), which may be also operative in neonatal liver (Pines *et al.*, 1976; Bashan *et al.*, 1979; Martin *et al.*, 1981), since term newborns showed normoglycaemia at 3 h *post partum*. In contrast, preterm newborns increased their blood glucose concentration between 3 and 6 h *post partum* (Table 1), clearly owing to an increase in the rates of glucose production by gluconeogenesis (Table 2), since no differences were observed in the rates of glycogenolysis between the two time periods (16 and 15.7 $\mu\text{mol/min}$ per 100 g body wt. at 3 and 6 h *post partum* respectively). Actually, the increase in gluconeogenesis (Table 2) in preterm newborns is probably the result of a greater activity of liver and kidney phosphoenolpyruvate carboxykinase (Table 3).

A noteworthy observation is that, although at all the time points studied kidney phosphoenolpyruvate carboxykinase activity in term newborns was higher than in preterm newborns, its induction between 0 and 6 h in term newborns was only by 25%, whereas

in preterm newborns it was induced by 72% of the activity present at birth. Since blood lactate concentrations in preterm newborns were higher than in term newborns at all time points studied (Table 1), it is reasonable to suggest that the metabolic acidosis observed in preterm newborns is an operative mechanism of induction of the renal phosphoenolpyruvate carboxykinase activity in the newborn rat from 1 day before birth, as has been shown for the adult rat (Tilghman *et al.*, 1976; Iynedjian *et al.*, 1975).

We have reported that during the first 2 h *post partum* blood lactate was oxidized to yield energy rather than being converted into glucose (Medina *et al.*, 1980). Furthermore, we noted that the delay in utilization and/or increased production of lactate in the premature newborn rat was due to the transient hypoxia undergone by these newborns during the first 1 h *post partum* (Cuezva *et al.*, 1981). From the results in Table 2, it is clear that only 10–20% of the lactate turned over is converted into glucose. These results confirm and quantify our previous finding that, during the first postnatal hours, blood lactate is mainly an oxidizable metabolite rather than a precursor for glucose synthesis (Medina *et al.*, 1980). The findings of Hellman *et al.* (1982), in which blood lactate was shown to cross the blood/brain barrier and to be actively metabolized in the brain of the perinatal dog, with its utilization highly increased by hypoglycaemia, strongly suggests that the lactate produced by the muscle out of its glycogen reserves (Snell & Walker, 1973) supports almost all the energy requirements of the preterm and term neonatal brain until glucose and ketone bodies, the main energy substrates of the neonatal brain (Hawkins *et al.*, 1971; Spitzer & Weng, 1972; Gregoire *et al.*, 1978), become available.

To sum up the main points, we have quantified the contribution of the gluconeogenic pathway to the glucose availability in the early postnatal period of term and preterm newborn rats, demonstrating a delayed induction of phosphoenolpyruvate carboxykinase activity in the preterm liver which results in lower rates of gluconeogenesis in this group of newborns. Also, the rates of lactate turnover in both groups have been measured, showing that the lactate utilized by the gluconeogenic pathway is only 20% of that turned over. A complete evaluation of the degree of utilization of blood lactate in the neonatal rat tissues remains to be established.

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