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Lipoprotein lipase, hepatic lipase, and carnitine in premature infants

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SUMMARY Twenty six preterm infants were studied at the age of 2, 7, and 26 days. The activities of lipoprotein and hepatic lipase in plasma taken 15 minutes after a heparin bolus of 100 IU/kg had been given and the concentrations of carnitine in serum and urine were measured. The mean gestational age was 31 weeks (range 26–35 weeks) and birth weight 1580 g (range 840–2280 g). Thirteen infants weighed under 1500 g at birth (very low birth weight), 20 were of appropriate weight for gestational age and six were small for gestational age. Lipoprotein lipase activity was higher in the preterm infants of appropriate weight than in the infants of very low birth weight and those who were small for gestational age. At the age of 2 or 7 days the activity of lipoprotein lipase in the preterm infants (mean (SEM) 46·2 (4·3) μmol free fatty acid/ml/hour) was, however, higher than in term infants and adults. Multivariate regression analyses showed that weight and relative birth weight together explained 58% of the variance of lipoprotein lipase activity but only 3% of the variance of hepatic lipase activity. Serum carnitine concentration was lower in the preterm infants than in term infants. Urinary excretion of carnitine increased progressively with age but was independent of serum concentration and carnitine intake. Urinary excretion of total carnitine was significantly greater in the infants who were small for gestational age (mean (SEM) 754 (203) nmol/mg of creatinine, n=6) than in the infants of appropriate weight (161 (22·0) nmol/mg of creatinine, n=12) but acyl/free carnitine ratio was smaller in the infants who were small for gestational age than in infants of appropriate weight (0·56 *v* 5·5). The results indicate that the slow elimination of fat from the circulation in preterm infants less mature than 32 weeks of gestation can hardly be explained by low lipoprotein lipase activity.

Carbohydrate supply through the placenta ceases after birth, and the glycogen stores of the infant are quickly depleted. Fat from adipose tissue and breast milk then becomes the infant's main source of energy. In very low birthweight infants and in infants small for gestational age adipose tissue depots are limited, and elimination of fat from the circulation is impaired. In addition, fat absorption from breast milk is only 85–90% due to deficiencies in pancreatic lipase and bile salts. Also the intake of breast milk is severely limited by various diseases that are typical of preterm infants. Hence, infants of very low birth weight and those who are small for gestational age may develop energy shortage during their first weeks of life.

Lipoprotein lipase is the rate limiting enzyme for the hydrolysis of triglycerides in plasma lipoproteins.[1] In infants, postheparin lipolytic activity (PHLA) has been used as a measure of lipoprotein lipase activity.[2 3] In preterm infants less mature than 27 weeks of gestation PHLA is less than 30% of the PHLA found in more mature preterm and term infants.[2–4] Our earlier results, however, indicate that lipoprotein lipase activity, measured with a specific method, is higher in preterm than term infants, and as high in term infants as in adults.[5 6]

Hepatic lipase forms a substantial part of PHLA.[7] The function of hepatic lipase in triglyceride metabolism is not known for certain.[1 8] In term and preterm infants the heptic lipase activities are about three times the lipoprotein lipase activities, and the two lipase activities vary independently.[5 6] Neither enzyme activity has been systematically studied in infants of very low birth weight and those who are small for gestational age.

Carnitine is essential for the facilitated transport of long chain free fatty acids across the mitochond-

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rial membrane for β oxidation.[9] Newborn infants may, however, be incapable of sufficient carnitine synthesis.[10] During carnitine free parenteral nutrition or enteral feeding with soybean based formula preterm infants have reduced blood, urinary, and tissue concentrations of carnitine combined with impaired fatty acid oxidation and ketogenesis.[11] The adequacy of carnitine intake from breast milk has not been studied in preterm infants.

To investigate the main determinants of fat utilisation in preterm infants we measured the activities of lipoprotein and hepatic lipase in post-heparin plasma and the concentrations of carnitine in plasma and urine of infants of very low birth weight and those who were small for gestational age and of a comparison group consisting of other preterm infants.

Subjects and methods

We studied 26 preterm infants, 12 girls and 14 boys. The purpose of the investigation was explained to the parents and studies were carried out with their consent. The experimental protocol had been approved by the ethical committee at this hospital. Sixteen of the 25 mothers were healthy and had an uncomplicated pregnancy. The gestational ages of the infants ranged from 26 to 35 weeks. Thirteen infants were less mature than 32 weeks of gestation, and three of them weighed more than 1500 g. The birth weights ranged from 840 to 2280 g and the relative birth weights from −3·2 to +1·4 SD units. Relative birth weight refers to the deviation of the individual birth weight from the mean birth weight of the gestational age group divided by the corresponding standard deviation.[12] Twenty infants had an appropriate weight for gestational age (relative birth weight within ±2·0 SD units) and six infants were small for gestational age (relative birth weight <−2·0 SD units). Thirteen infants had very low birth weight (birth weight <1500 g): two were more mature than 32 weeks of gestation and four were both small for gestational age and of very low birth weight. Because gestational age is somewhat unreliable we divided the infants into groups according to their birth weights. The table shows the clinical data of the preterm infants.

FEEDING

All infants received pasteurised breast milk from a milk bank, but 20 infants also received 10% glucose intravenously (mean duration 12·5 days). None received fat emulsion or amino acids. The mean amount of breast milk was 34 ml/kg/day (range 0–91) and the mean number of calories 0·17 MJ/kg/day (range 0·10–0·34) during the first three days of life, 159 ml/kg/day (range 31–220) and 0·48 MJ/kg/day (range 0·25–0·62) during 6–8 days of life, and 185 ml/kg/day (range 90–210) and 0·53 MJ/kg/day (range 0·33–0·59) during 25–27 days of life. All infants received supplementation of vitamins A, B12, C, D, and E, and folic acid from the age of

Table *Clinical data of preterm infants studied (n=26)*

	Infants of appropriate weight for gestational age		*Infants who were small for gestational age*	
	<1500 g (n=9)	*>1500 g (n=11)*	*<1500 g (n=4)*	*>1500 g (n=2)*
Gestational age (weeks) (mean(range))	29·3 (27·4–30·9)	32·6 (29·9–34·6)	30·7 (26·4–34·6)	34·5 (34–35)
Birth weight (g) (mean (range))	1288 (1080–1470)	1941 (1530–2260)	1171 (840–1460)	1820 (1780–1860)
Relative birth weight (SD) (mean (range))	−0·9 (−1·4 to 1·4)	−0·5 (−1·9 to 1·3)	−2·7 (−3·2 to −2·2)	−2·3 (−2·5 to −2·1)
Apgar score <7 at 1 minute	9	3	4	–
Boys/girls	6/3	6/5	1/3	1/1
No infants who had:				
Mechanical ventilation	9	3	4	–
RDS*/BPD†	9/2	2/–	1/1	–/–
Antibiotic treatment	9	5	3	1
Dopamine infusion	8	–	2	–
Phototherapy (prophylactic)	9	11	3	1
Ductus arteriosus				
Indomethacin treatment	4	–	1	–
Operation	–	–	1	–

*RDS=Respiratory distress syndrome.
†BPD=Bronchopulmonary dysplasia.

3 days, and iron (3–4 mg/kg/day) from the age of 2 weeks. On average, weight at the age of 7 days was 9% lower than at birth. The mean gain of weight by the age of 26 days was 12·0 g/day (range 2·0–20·0 g/day).

BLOOD AND URINARY SAMPLES

On the 2nd, 7th, and 26th day of life a blood sample was taken through an indwelling peripheral vein catheter for measurement of total and free carnitine and basal plasma activities of lipoprotein and hepatic lipases. On average, the infants had fasted two hours before sampling. On the 2nd day of life a heparin bolus of 100 IU/kg (Medica, Helsinki, Finland) was injected through the catheter of those 11 infants who had reached stable ventilation (pH>7·35, pCO_2<6·6 kPa, FiO_2<0·45, PaO_2>5·9 kPa) and haemodynamics (mean blood pressure >45 mm Hg, normal urinary flow, and serum urea nitrogen <15 mmol/l) and who did not have abdominal distension, intraventricular haemorrhage, or hyperbilirubinaemia. Fifteen minutes after the injection a blood sample was taken for the measurement of lipase activities. At the ages of 7 and 26 days lipase activities were measured for the first time from 14 and one infants and for the second time from six and seven infants, respectively. As we have found previously the infants showed no signs of a tendency to bleed or other side effects as a result of the heparin administration.[5 6 13 14] Urine was collected for 24 hours between the 1st and 2nd, 7th and 8th, and 26th and 27th days of life. The

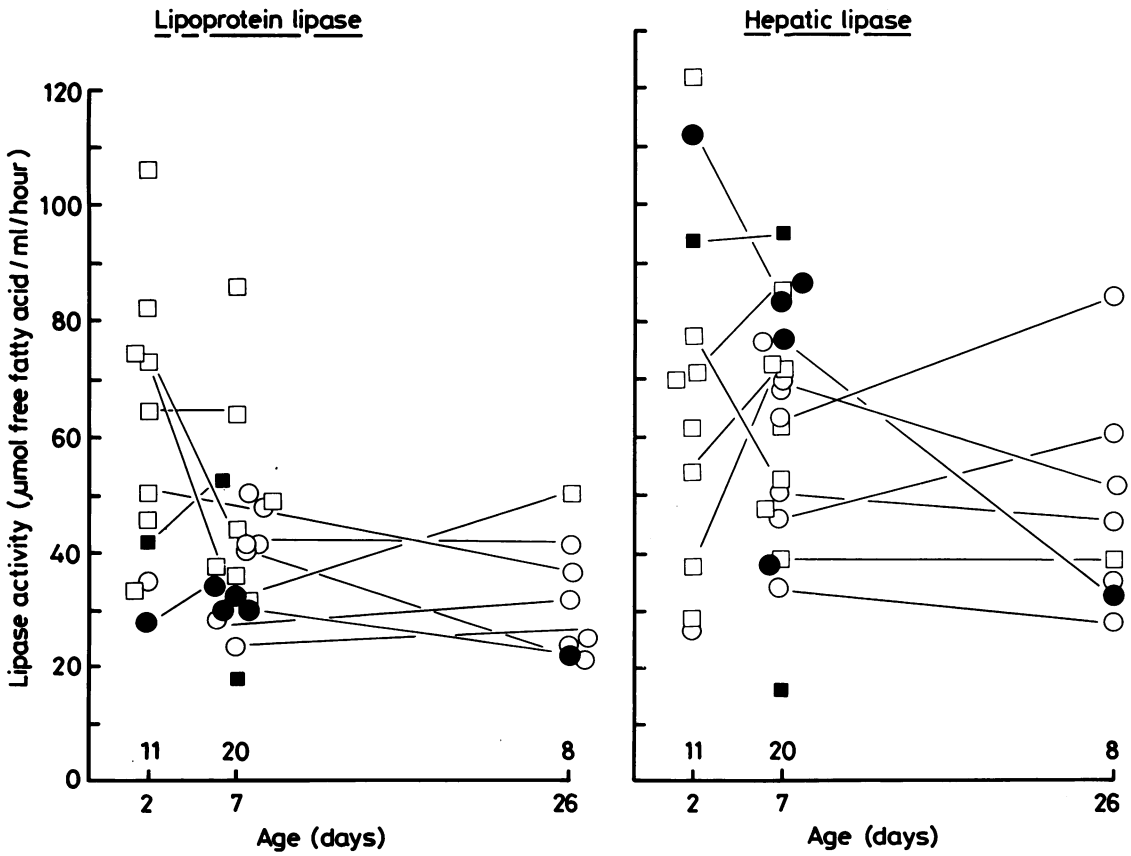

Fig 1 *Activities of lipoprotein lipase and hepatic lipase at 2, 7, and 26 days of age. Inset numbers refer to the numbers of subjects. Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g. The repeated measurements are connected with lines.*

samples were used for the determinations of total and free carnitine concentrations.

BIOCHEMICAL ASSAYS

All blood samples were collected into chilled tubes kept in ice. They were immediately centrifuged, and the plasma and serum obtained were stored at −20°C until assayed within a month. Urine was collected during 24 hours into bottles and kept in a refridgerator. The urinary volumes collected were then measured, and the urinary samples were stored at −20°C until assayed within a month.

Total and free carnitine concentrations were measured with the radioisotopic method of McGarry and Foster[15] modified according to Novak *et al.*[16] Urinary and milk samples were first sonicated, then diluted with 4 volumes of distilled water, and resonicated. Part of the sample was used for the measurement of free carnitine concentration. The rest of the sample was first hydrolysed in 0·1 M potassium hydroxide at 37°C for 60 minutes, and then neutralised and sonicated for the measurement of total carnitine. Urinary carnitine excretion was expressed as nmol/mg of creatinine. Acylcarnitine was calculated by subtracting free carnitine from total carnitine.

Lipoprotein and hepatic lipase activities of postheparin plasma were measured with the immunochemical method of Huttunen *et al*[7]: lipoprotein lipase was measured after inactivating hepatic lipase with a specific antiserum produced in rabbits against purified human postheparin plasma hepatic lipase. Hepatic lipase was measured in 1 M sodium chloride, a concentration that inactivates lipoprotein lipase, no serum was added. The substrate was acyl-1-^{14}C labelled triolein emulsion prepared by sonication.

STATISTICAL ANALYSES

Statistical analyses were performed with the BMDP statistical software package.[17] Two way analyses of variance for the repeated measurements of carnitine were performed with time as a within factor. Wilcoxon test and paired *t* test were used for comparing the repeated measurements of lipase activities. The Mann-Whitney test and unpaired *t* test were used for comparing lipase activities and serum and urinary carnitine concentrations between infants of very low birth weight, those who were small for gestational age, and other preterm infants. In addition, simple linear regression analyses were computed between serum and urinary concentrations of carnitine, lipases, and the other relevant variables. Multivariate regression analyses were then performed to sort out the main factors explaining the variation of lipoprotein lipase activity and carnitine concentration.

Results

POSTHEPARIN PLASMA LIPOPROTEIN AND HEPATIC LIPASE ACTIVITIES

Fig 1 shows lipoprotein and hepatic lipase activities measured at the age of 2, 7, and 26 days. Lipase activities were measured in six infants at 2 and 7 days of age and in seven infants at 7 and 26 days of age. When comparing the repeated measurements the mean activities of both lipases were found to be independent of postnatal age ($p>0·3$).

The activities of lipoprotein and hepatic lipase, measured for the first time at the age of 2 and

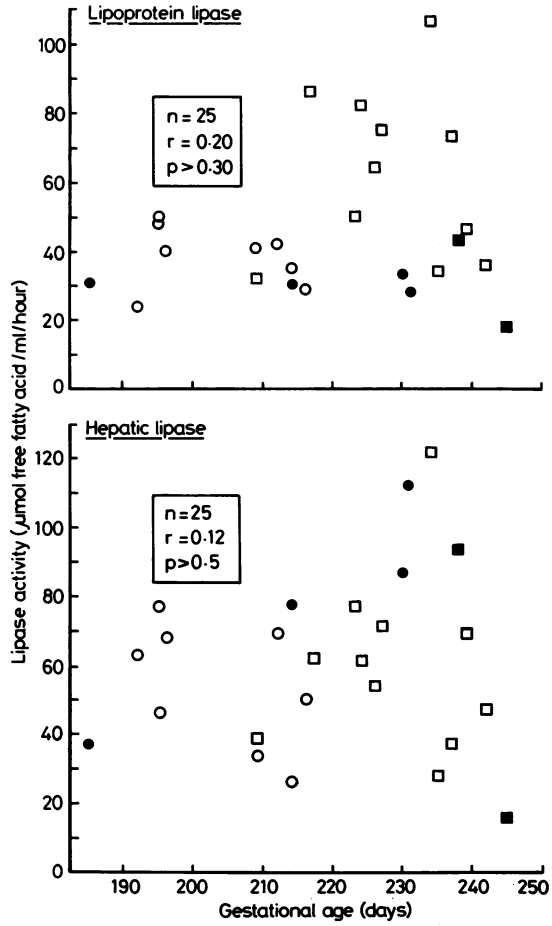

Fig 2 *Activities of lipoprotein lipase and hepatic lipase, measured for the first time at 2 or 7 days of age plotted as a function of gestational age. Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g.*

7 days, are plotted as a function of gestational age (fig 2). Both lipase activities were found to be independent of gestational age. Nevertheless, lipoprotein lipase activity correlated positively with birth weight ($r=0{\cdot}62$, $p<0{\cdot}001$) and relative birth weight ($r=0{\cdot}63$, $p<0{\cdot}001$) (fig 3a). The exclusion of infants who were small for gestational age resulted in a stronger correlation ($r=0{\cdot}67$, $p<0{\cdot}001$) between lipoprotein lipase activity and birth weight (fig 3b). Hepatic lipase activity correlated with neither measure.

The multivariate regression analyses showed that birth weight and relative birth weight together explained 58% of the variance of lipoprotein lipase activity but only 3% of the variance of hepatic lipase activity in our preterm infants. When the effects of birth weight and relative birth weight were removed, however, the partial correlation between gestational age and lipoprotein lipase activity (see fig 2 (top)) was $-0{\cdot}57$ ($p<0{\cdot}01$); hepatic lipase remained independent of gestational age.

When the infants who were small for gestational age were excluded, the mean (SEM) lipoprotein lipase activity in the very low birth weight infants (38·6 (3·2) μmol free fatty acid/ml/hour) was lower ($p<0{\cdot}02$) than in the infants weighing more than 1500 g (62·2 (7·3) μmol free fatty acid/ml/hour) (fig 3b) whereas the mean hepatic lipase activities were similar (54·3 (6·4) μmol free fatty acid/ml/hour for the very low birth weight infants and 60·6 (7·7) μmol free fatty acid/ml/hour for the other infants). Eleven of the 13 infants of very low birth weight studied were less mature than 32 weeks of gestation and 10 of the 13 infants weighing more than 1500 g were more mature than 32 weeks of gestation. Also, the mean (SEM) lipoprotein lipase activity was lower ($p<0{\cdot}002$) in the infants who were small for gestational age (30·5 (3·2) μmol free fatty acid/ml/hour) than in the infants of appropriate weight (52·3 (5·2) μmol free fatty acid/ml/hour) (fig 3a) whereas the mean hepatic lipase activities were similar (70·7 (15) μmol free fatty acid/ml/hour

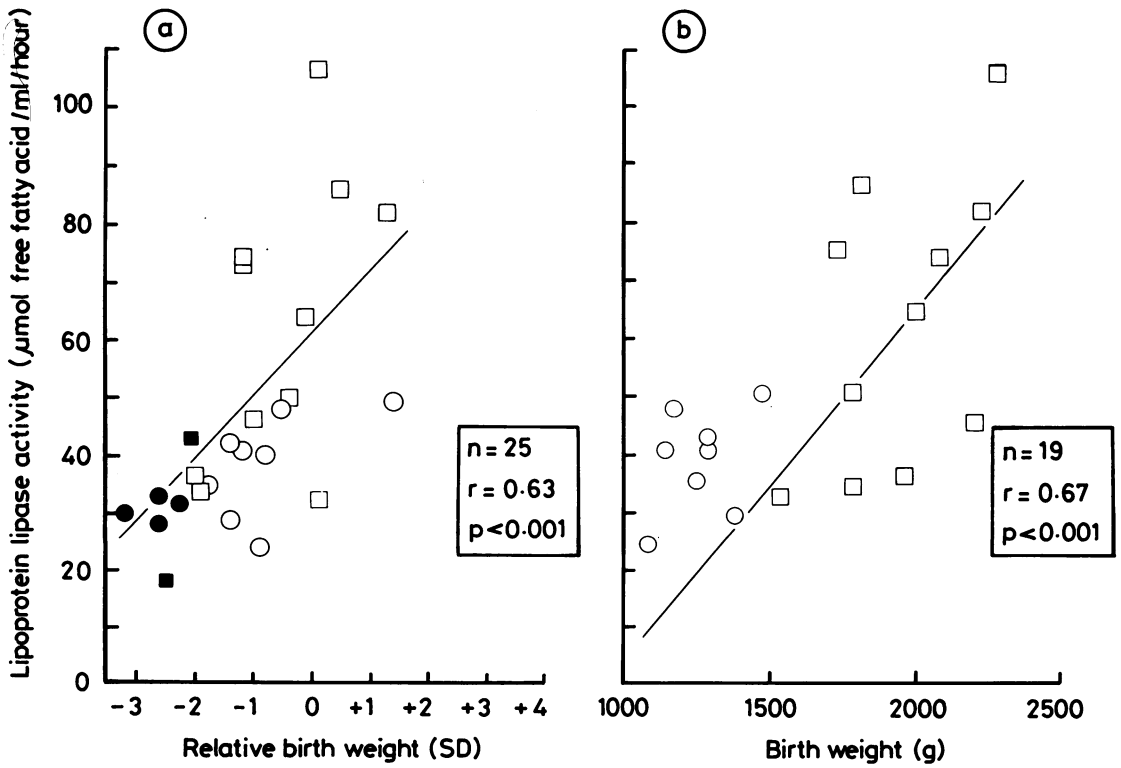

Fig 3 *Activity of lipoprotein lipase, measured for the first time at 2 or 7 days of age plotted as a function of relative birth weight (a) and birth weight (b). Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g.*

for the infants who were small for gestational age and 57·9 (5·2) μmol free fatty acid/ml/hour for the infants of appropriate weight).

SERUM CONCENTRATION AND URINARY EXCRETION OF CARNITINE

Serum total and free carnitine concentrations first decreased ($p<0·03$) and then increased during the first 26 days of age (fig 4a); the increase was not significant. Urinary excretion of total and free carnitine and acylcarnitine increased ($p<0·01$) progressively with age from 7 to 26 days (fig 4b).

The multivariate regression analyses showed that urinary excretions of total and free carnitine were independent of the serum concentration of total carnitine and of daily carnitine intake calculated from the ingested milk volume and the concentration of total carnitine (51·6 nmol/ml) in bank breast milk. Urinary excretion of total and free carnitine, however, correlated negatively with relative birth weight at the age of 2 days ($r=-0·59$, $p<0·03$ and $r=-0·57$, $p<0·04$) and 7 days ($r=-0·65$, $p<0·003$) and $r=-0·61$, $p<0·006$) but were independent of birth weight and gestational age. Fig 5 shows the negative correlation between total carnitine excretion and relative birth weight at 7 days of age.

At the age of 7 days urinary excretion of total carnitine was larger ($p<0·001$) in the infants who were small for gestational age (mean (SEM) 754 (203) nmol/mg of creatinine, n=6) than in the infants of appropriate weight (161 (22) nmol/mg of creatinine, n=12) (fig 5). The mean urinary acyl/free carnitine-ratio was 0·56 (range 0·16–1·0) in the infants who were small for gestational age and 5·5 (range 1·5–15) in the infants of appropriate weight. Serum concentrations of total carnitine, however, were not different in the infants who were small for gestational age (mean (SEM) 26·5 (3·5) nmol/ml,

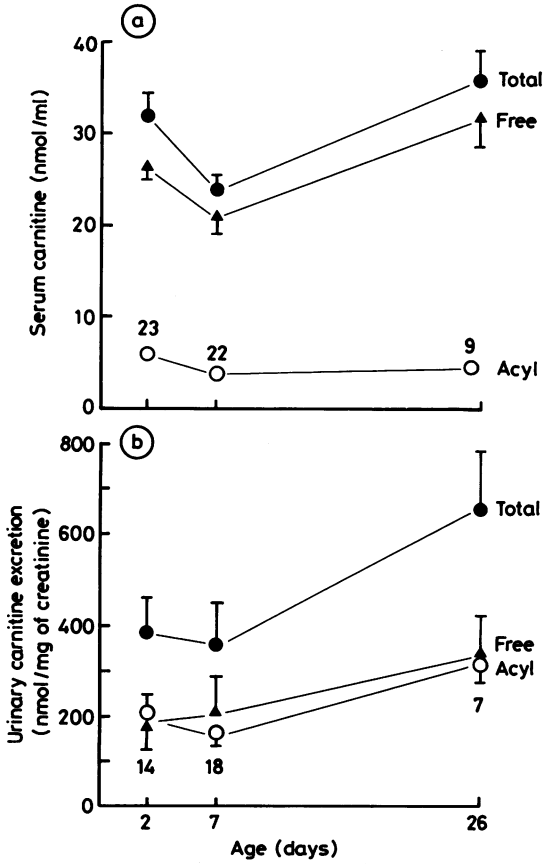

Fig 4 *Serum (a) and urinary (b) concentrations of total and free carnitine and acylcarnitine at 2, 7 and 26 days of age. Numbers close to the curves refer to the numbers of subjects.*

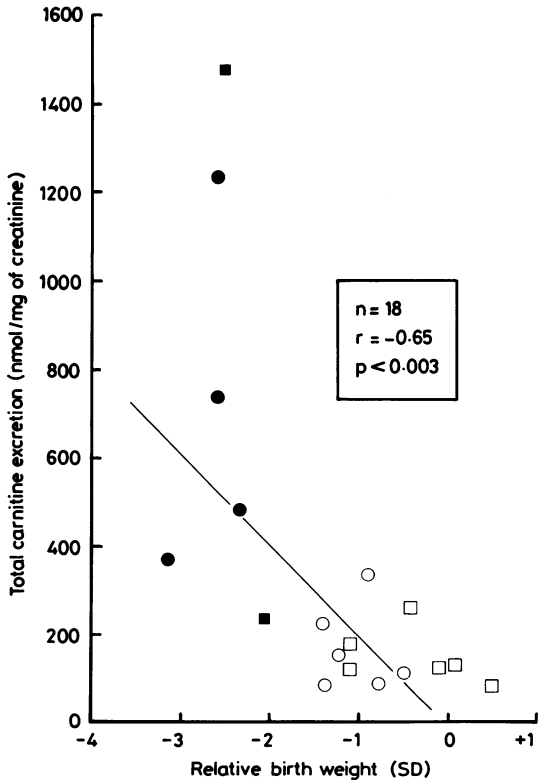

Fig 5 *Total carnitine excretion as a function of relative birth weight at 7 days of age. Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g.*

n=6) and those of appropriate weight (22·7 (1·7) nmol/ml, n=12).

Discussion

Postheparin lipolytic activity[2–4] and fat elimination tests[18] suggest that lipoprotein lipase activity may be low in preterm infants. We found, however, that the mean (SD) activity of postheparin plasma lipoprotein lipase, measured with a specific method, was appreciably higher in our three groups of preterm infants (46·2 (22·0) μmol free fatty acid/ml/hour) than in more mature preterm infants[5] (26·8 (13·3) μmol free fatty acid/ml/hour), term infants[6] (16·0 (6·8) μmol free fatty acid/ml/hour), and adults[6] (17·5 (6·3) μmol free fatty acid/ml/hour). We also found that the mean activity of postheparin plasma lipoprotein lipase in the very low birth weight and small for gestational age infants was lower than in the infants of appropriate weight. Hence, our results agree with the finding that the elimination of fat in infants less mature than 32 weeks of gestation or infants who are small for gestational age is slower than in infants of appropriate weight.[18]

We measured the activity of postheparin plasma lipase 15 minutes after a heparin bolus of 100 IU/kg whereas the other investigators have measured PHLA 5–10 minutes after a heparin bolus of 10 IU/kg.[2–4] Stahl *et al* have speculated that our large bolus of heparin not only releases the endothelial lipoprotein lipase but also stimulates lipase synthesis within adipose and muscle tissues,[4] which results in higher lipase activities. In vitro, however, heparin neither stimulates liprotein lipase synthesis nor activates the lipase.[19–20] Instead heparin releases the functional lipoprotein lipase from the endothelial vascular surface and intracellular pool.[21] Also, intralipid and very low density lipoprotein particles are capable of releasing functionally active intracellular lipoprotein lipase.[22] Whatever the origin of the lipoprotein lipase activity released by 100 IU/kg heparin, in adults it correlates with the elimination of fat emulsion injected intravenously.[23]

Poor elimination of the fat infused into the circulation of preterm infants results in triglyceridaemia, the extent of which is in inverse proportion to gestational age.[4 18] In preterm infants less mature than 27 weeks of gestation, PHLA is less than 30% of the PHLA found in more mature preterm and term infants.[2–4] This had led to the suggestion that lipoprotein lipase activity increases with gestational age. In our preterm infants postheparin plasma lipoprotein lipase activity was independent of gestational age but correlated positively with birth weight. Gestational age and birth weight are, however, strongly interdependent during the last trimester of pregnancy. When the effects of birth weight and relative birth weight were removed by statistical means, lipoprotein lipase correlated negatively with gestational age. This means that lipoprotein lipase activity decreases with gestational age, contradicting the earlier suggestions.[2–4 18] Thus the negative correlation of lipoprotein lipase with gestational age may provide a partial explanation for our finding that lipoprotein lipase activity was higher in preterm than term infants.

In animals lipoprotein lipase activity increases with postnatal age.[24] In preterm infants, however, we found no increase of postheparin lipoprotein lipase activity with age, although an increase of lipoprotein lipase activity has been documented during total parenteral nutrition in term infants.[13]

Postheparin plasma lipoprotein lipase activity correlates with birth weight and relative birth weight, in agreement with the positive correlation between the peak PHLA and body weight.[4] In adipocytes lipoprotein lipase activity correlates with fat tissue weight.[25] Perhaps the poor elimination of the fat infused in preterm infants less mature than 32 weeks' gestation is explained by low birth weight instead of young gestational age. Animal studies on fat deposition indicate that lipoprotein lipase hydrolyses fatty acids and glycerol from chylomicron triacylglycerol; fatty acids are then transported into the adipocytes for re-esterification to cellular triglycerides.[26]

In our preterm infants the mean (SD) postheparin plasma activity of hepatic lipase (60·0 (26·0) μmol free fatty acid ml/hour) was as in term infants (54·2 (18·0) μmol free fatty acid/ml/hour)[6] but about three times higher than in adults (23·1 (11·0) μmol free fatty acid/ml/hour).[6] There is evidence that hepatic lipase participates in the metabolism of the phospholipids and cholesterol of high density lipoproteins by increasing the flux of free cholesterol into the target tissues.[8] In vitro, hepatic lipase is, however, also capable of hydrolysing triglycerides and the phospholips of fat emulsion particles.[27] Also, in familial lipoprotein lipase deficiency the intact hepatic lipase hydrolyses triglycerides in very low density lipoproteins.[28] High hepatic lipase activity may thus contribute to the hydrolysis of triglycerides in infants. The importance of high hepatic lipase activity, however, in the lipid metabolism of preterm infants cannot be evaluated at the moment because the function of hepatic lipase is not known.

Newborn infants may be incapable of sufficient carnitine synthesis and are therefore dependent on nutritional sources of carnitine.[9] Our preterm infants were principally fed with breast milk. Their daily carnitine intake was 1·6, 8·2, and 9·6 μmol/kg at the age of 2, 7, and 26 days. Thus the intake at the

age of 7 and 26 days was as in term infants and adults.[29] The mean serum concentration of total carnitine in our preterm infants, however, was much lower than in breast fed term infants at the age of 2 (59·3 nmol/ml) or 6 months (62·5 nmol/ml),[29] although the serum carnitine concentration in cord blood is usually higher in preterm than term infants.[16]

At the age of 7 days in our infants of appropriate weight urinary carnitine excretion and acyl/free carnitine-ratio was as in preterm infants.[11] Carnitine excretion decreased with increasing relative birth weight: it was lower in appropriate weight infants than in infants who were small for gestational age. In addition, urinary acyl/free carnitine-ratio was low in the infants who were small for gestational age, which means that most of the carnitine they excreted in urine was free carnitine, as is the case in trauma patients and in renal tubular diseases.[30]

In conclusion, our study showed that lipoprotein lipase activity in very low birth weight, small for gestational age, and appropriate weight preterm infants was higher than in more mature preterm infants, term infants, and adults. This indicates that the slow elimination of fat from the circulation in preterm infants less mature than 32 weeks' gestation can hardly be explained by low lipoprotein lipase activity. Instead, the low serum carnitine concentrations of preterm infants and the large excretion of carnitine, especially in infants who were small for gestational age, might explain the slow elimination of fat.

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