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Adipose tissue
blood triglyceride clearing
fetus
heart
lipoprotein lipase
lung
newborn
surfactant

Lipoprotein Lipase Activity and Blood Triglyceride Levels in Fetal and Newborn Rats

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Summary

Lipoprotein lipase activity in lung and heart was studied in fetal (17–22 days of gestation) and newborn rats from the day of birth until 30 days of age. Enzyme activity in epididymal, omental, and parametrial adipose tissue was tested after 18 days of age. Blood triglyceride levels were measured at all ages from 17 days *in utero* until 30 days after birth.

The developmental pattern of lipoprotein lipase differed markedly in lung and heart. Although lipoprotein lipase activity was 4 to 5 times higher in adult rat heart than in lung (30–40 U/g in heart vs. 8–11 U/g in lung), the activity was almost completely absent from fetal heart and was very low during the first 3 days after birth. Lipoprotein lipase reached 60–70% of adult activity at 6 days and remained at that level until 19 days after birth; adult activity levels were reached at 24 days. In the lung, contrary to the heart, lipoprotein lipase activity was high in the fetus (84% of adult activity), decreased immediately after birth to 45% of adult activity at 2 days, and remained at that level up to 15 days after birth. Enzyme activity started to rise again at 15 days and reached adult levels at 21 days of age. Adipose tissue was present in trace amounts before the age of 2 weeks. In the three fat depots tested, lipoprotein lipase activity was 50% lower than in adults between 20 and 30 days after birth. Blood triglyceride levels increased 4-fold between 2 to 10 hr after birth and remained elevated during the first 3 days after birth.

Speculation

The triglyceridemia that starts in the immediate postnatal period and lasts for several days in the rat probably results from the combination of high fat intake and low clearing ability of the extrahepatic tissues.

In addition to its role in clearing circulating triglyceride, lipoprotein lipase may play a role in the growth and maturation of individual organs. The present study shows that lipoprotein lipase activity is high in fetal lung during the period of marked surfactant synthesis and suggests that circulating triglyceride-fatty acids are used by the fetal lung for surfactant synthesis.

Triglycerides, the main component of dietary fat, provide more than 50% of the caloric intake of the newborn. Triglycerides of dietary origin are transported in the circulation in large particles—the chylomicrons. There is good evidence that chylomicron triglycerides are rapidly cleared from the circulation through the action of the enzyme lipoprotein lipase (29, 33). The function of this enzyme is to hydrolyze plasma triglycerides and thereby facilitate the uptake of their constituent fatty acids by the extrahepatic tissues of the body. Lipoprotein lipase acts on plasma triglycerides at the luminal surface of the endothelial cells (29, 33) that line the capillaries of extrahepatic tissues such as heart (3), lung (18, 19), and adipose tissue (33).

Recent studies suggest that triglyceride clearing is markedly impaired in premature infants (1); this could be directly related to low levels of plasma postheparin lipolytic activity at this age (32). No information is available at present on the level of lipoprotein lipase activity in tissues of premature and term infants. Because intralipid, a high calorie isotonic fat emulsion (16, 30), similar to chylomicrons (16), is used with increasing frequency in intravenous nutrition of sick premature infants (12, 13), it is of great interest to know more about the clearing ability of this age group.

In addition to its role in clearing circulating triglyceride, lipoprotein lipase may have a special function in the growth and maturation of individual organs.

The purpose of the present study was to investigate lipoprotein lipase activity in heart, lung, and adipose tissue of developing rats and the relationship between enzyme activity and blood triglyceride concentration.

MATERIALS AND METHODS

ANIMALS

Sprague-Dawley rats were used in these experiments. The rats were mated during the night and examined the next morning for evidence of impregnation (vaginal plug formation); the duration of pregnancy was calculated from that morning. Throughout pregnancy and lactation the rats had free access to food, Purina laboratory chow (Ralston Purina Co., Saint Louis, MO) and water.

PREPARATION OF TISSUES FOR LIPOPROTEIN LIPASE ASSAY

Fetal Rats. Seventeen- to 22-day pregnant rats were killed by decapitation and the blood was collected for plasma triglyceride determination. The uteri were clamped *in situ*, resected, and transferred to beakers containing ice-cold saline. The fetuses were delivered and individually weighed and cord blood was immediately collected. The lungs and heart were removed under a dissecting magnifying glass, rinsed in ice-cold saline, and placed in 0.5–2.0 ml 0.025 M NH_3-HCl buffer containing heparin (1 U/ml). Tissues from several fetuses were pooled to give a combined weight of 100–200 mg.

Newborn Rats. The rats were weighed and decapitated; after collection of blood the lungs and heart were dissected, rinsed, and placed in buffer. Adipose tissue, epididymal, parametrial and omental, were collected when present. The stomach was checked for the presence of food to ensure that all pups were well fed.

PREPARATION OF ACETONE-ETHER POWDERS

The tissues were minced and homogenized with a Teckmar Tissumizer (model SDT 182 N, Teckmar Co., Cincinnati, OH). The homogenates (in 2-3 ml HN_3-HCl buffer) were then poured into 80 ml ice-cold acetone. The tissue constituents insoluble in acetone were collected by filtration through Whatman #1 paper on a Buchner funnel. In order to increase the mass of precipitate, 80 mg of bovine plasma albumin in 0.5 ml of 0.85% NaCl (pH 8.1) were added to the homogenate-acetone mixture before filtration. The tissue residue was washed with 100 ml cold acetone, 100 ml acetone at room temperature, and finally 100 ml diethyl ether

at room temperature. The defatted preparations were dried in vacuo at 0°and stored at −20° *in vacuo*. There was no loss of lipolytic activity during storage at −20° for 7–14 days; lipolytic activity was, however, lost rapidly during storage at 0–4°.

LIPOPROTEIN LIPASE ASSAY

The acetone powders were solubilized by homogenization in cold 0.025 M NH_3-HCl buffer, pH 8.1, containing heparin (1 U/ml) and kept on ice until assayed within 15–30 min. Lipoprotein lipase activity was measured by the amount of triglyceride hydrolyzed to glycerol and free fatty acids at pH 8.1.

PREPARATION OF TRIGLYCERIDE EMULSION

One hundred fifty micromoles triglyceride (corn oil or triolein), 4.0 μmol diolein, 2 μmol monolein, 2.0 μmol oleic acid, 6.0 μmol lecithin, and 1 μmol cholesterol were mixed with [2-^{3}H]glyceryl-triolein (Amersham-Searle TRA 172, batch 14) and [1-^{14}C]glyceryl-tripalmitin (Amersham-Searle CFA 64, batch 30); the solvents (chloroform or benzene) were evaporated at 45–50° under a stream of nitrogen. Glycerol (1.5 ml of 99%) and albumin (1.5 ml of 4%) dissolved in saline were added and mixed vigorously for 1–2 min in a Vortex shaker followed by sonication with a Polytron PCU-2-110 sonifier (Brinkman Instruments, Westbury, NY) at setting 10 for two periods of 30 sec. The lipid emulsion was then mixed with 2 ml rat serum and centrifuged at 50.000 *g* for 1 hr at 4° in a Sorvall OTD-65 ultracentrifuge. The lipid pellicle was separated and solubilized in 4% albumin solution at a triglyceride concentration of 60–100 mM and stored at 4°. The emulsion was stable for 2–4 weeks.

The assay system contained 2 mM doubly labeled ([2-^{3}H]glyceryl, [1-^{14}C]tripalmitin) triglyceride, 0.125 M Tris-HCl buffer (pH 8.1), 4% bovine plasma albumin (Armour Pharmaceutical Co., Chicago, IL, lot N 50402) and 100–200 μl of enzyme suspension (equivalent to 5–20 mg wet wt of tissue) in a final volume of 0.5 ml. The triglyceride emulsion was incubated for 30 min with rat serum (20 μmol triglyceride per ml serum) before addition to the assay mixture; the rat serum was heated for 10 min to 60° to inactivate lipases (7) before its incubation with the triglyceride emulsion. Heparin (Liquemin Sodium, Organon, West Orange, NJ) concentration was 1 U/0.5 ml reaction mixture. Incubation was 15–60 min at 37° in a Dubnoff shaking bath. The reaction was stopped by the addition of 2.5 ml Dole's extraction mixture (isopropanol:hexane:1 N H_2SO_4—4.0:1.0:0.1) and the lipids were extracted into hexane by a slight modification (5) of the method of Dole (8).

The amount of triglyceride hydrolized was measured by the decrease of triglyceride in the reaction mixture. Because the triglyceride substrate was labeled with [^{3}H]glycerol and [^{14}C]-palmitate, the decrease in glyceride could be measured by the change in ratio of ^{3}H to ^{14}C in the hexane extract of the assay medium. The amount of triglyceride hydrolyzed was calculated as the product of the percentage change in the ratio and the amount of triglyceride added to the assay medium. Radioactivity in the hexane extract was determined in an aliquot evaporated and dissolved in 10 ml of 4.2% RPI scintillator (Research Products International Corp., Elk Grove Village, IL) in toluene. Radioactivity was measured in a liquid scintillation spectrometer (Beckman model LS—3150 T) using the external standard method for quench corrections.

The triglyceride content of the lipid emulsions was measured by the method of Rapport and Alonzo (28). Plasma triglyceride concentration was measured enzymatically (35).

RESULTS

The weight of newborn rats increased from 5.27 ± 0.13 g at birth to 9.91 ± 0.16 g at 4 days and 42.42 ± 1.19 g at 21 days. The growth rate was slowest in the first 6 days after birth, an average of 1.25 g/day, and increased to 2.0 g/day between 6 and 21 days; it was highest after weaning, 4.73 g/day between days 21 and 30

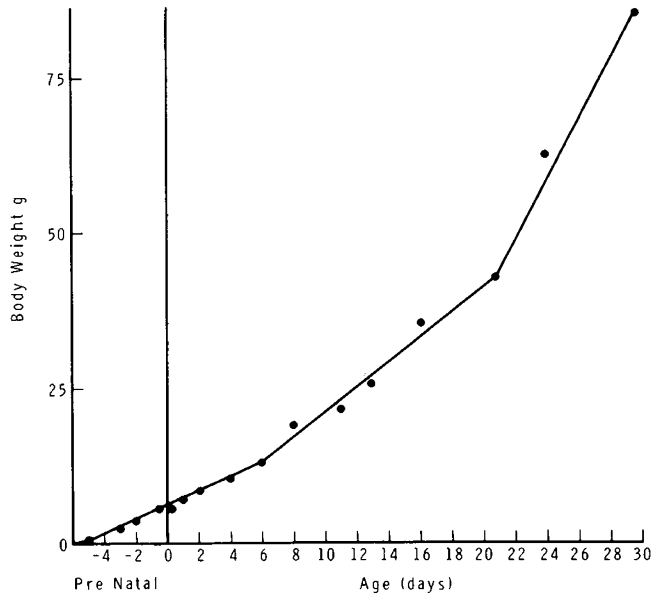

Fig. 1. Body weight of developing rats. Data are mean values for 6–10 animals at each age point.

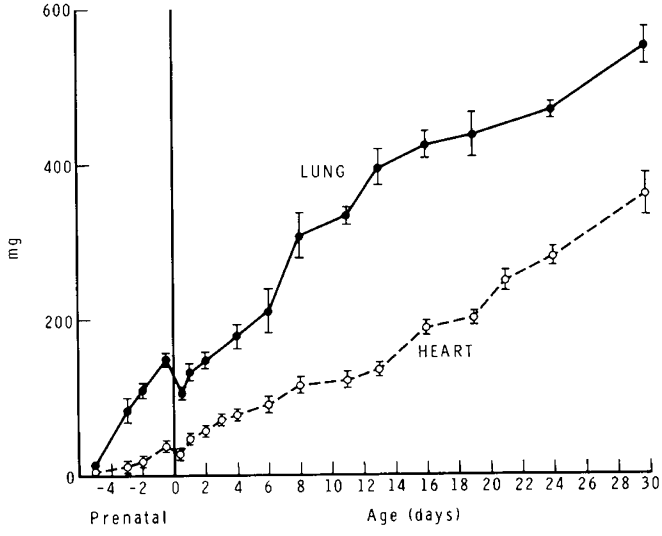

Fig. 2. Lung and heart weight of developing rats. Data are mean ± SE. There were 6–10 animals in each group.

(Fig. 1). Lung weight increased faster before and immediately after birth than heart weight (Fig. 2).

The characteristics of lipoprotein lipase in heart, lung, and adipose tissue were virtually identical in all age groups studied (Table 1). The enzyme activity had a pH optimum of 8.1; only traces of activity (less than 10% of the activity at pH 8.1) were present at pH 6.0; however, as much as 50% of maximal activity were present at pH 9.0 in all age groups studied. The activity was completely inhibited by 0.5 M NaCl (Table 1). Thirty to 50% of enzyme activity was lost during incubation in the absence of heparin. A comparison between triglyceride emulsion and doubly labeled dog chylomicron triglyceride (19) showed that lung lipoprotein lipase activity was identical whether emulsified or chylomicron triglyceride was used as substrate (Table 2). Failure to preincubate the triglyceride emulsion with serum led to a marked reduction in the enzyme activity of all tissues studied. The data indicate that the lipolytic activity in rat tissues of all ages studied had the characteristics of lipoprotein lipase—pH optimum above 8.0, dependence on heparin and serum, and complete inhibition by 0.5 M NaCl.

Table 1. *Characteristics of lipoprotein lipase activity of heart, lung, and adipose tissue during development*

Age	Lung		Heart		Adipose tissue[1]	
	pH optimum[2]	Effect of 0.5 M NaCl (% inhibition)	pH optimum	Effect of 0.5 M NaCl (% inhibition)	pH optimum	Effect of 0.5 M NaCl (% inhibition)
Fetal						
19–22 days	8.1	100	8.1	98		
3 days	8.1	98	8.1	99		
8 days	8.1	99	8.1	100		
16 days	8.1	100	8.1	98	8.1	100
24 days	8.1	99	8.1	100	8.1	99
Adult	8.1	100	8.1	100	8.1	100

[1] The adipose tissues studied were omental, epididymal, and parametrial. Identical results were obtained with the three different tissues.
[2] The effect of pH on lipolytic activity was measured in the range of 6.0–9.5.

Table 2. *Effect of triglyceride substrate on lipoprotein lipase activity in the developing lung*[1]

Age	% Adult activity	
	Chylomicron triglyceride	Emulsified triglyceride
Fetal		
19 days	61.4 ± 10	66 ± 8.0
21.5 days	76 ± 11	84 ± 12
Newborn		
6 hr	78 ± 12	78 ± 14
2 days	42 ± 7	45 ± 5.4
3 days	36 ± 10	43 ± 8.9
5 days	45 ± 10	46 ± 11
7 days	49 ± 8	43 ± 10
19 days	64 ± 12.1	65 ± 67

[1] Triglyceride substrate was present at a concentration of 2 mM doubly labeled (2^3H glyceryl-1 ^{14}C tripalmitin) chylomicron triglyceride (18) or serum activated triglyceride emulsion. Lipoprotein lipase activity was calculated as U/g; 1 U is equivalent to 1 μmole triglyceride hydrolyzed per hr; the activity of adult lung was 8–11 U/g. Details on the assay system are given under *Materials and Methods*. Data are mean ± SE.

Lipoprotein lipase activity in heart and lung and the concentration of blood triglyceride as a function of age are shown in Figure 3. Blood triglyceride concentration was 1.1 to 1.3 μmol/ml between 3 and 1 day before birth, and decreased to 0.7 ± 0.2 μmol/ml at birth. There was a sharp rise in the blood triglyceride level to 3.85 ± 0.25 μmol/ml 2 to 10 hr after birth. The triglyceride level decreased to 2.0 μmol/ml 1 day after birth and remained at that level for the following 2 days; it then decreased further to 1.2–1.3 μmol/ml and stayed at that level until 19 days after birth. Blood triglyceride levels were elevated again between day 21 and 24 before reaching adult levels of 1.05 ± 0.06 μmol/ml.

The developmental pattern of lipoprotein lipase differed markedly in lung and heart (Fig. 3). Although lipoprotein lipase activity was 4 to 5 times higher in adult rat heart than in lung (30–40 U/g in heart vs. 8–11 U/g in lung), the activity was almost completely absent from fetal heart and was very low during the first 3 days after birth. Lipoprotein lipase reached 60–70% of adult activity at 6 days and remained at that level until 19 days after birth. A 35% drop in activity (from 75 to 49% of adult activity) occurred at 21 days, the time of weaning; adult activity levels were attained at 24 days.

In the lung, contrary to the heart, lipoprotein lipase activity was high in the fetus (84% of adult activity); it decreased immediately after birth to reach 45% of adult activity at 2 days and remained at that level up to 15 days after birth. Enzyme activity started to increase again at 15 days and reached adult levels at 21 days of age (Fig. 3).

Adipose tissue, epididymal, parametrial and omental, were present in small amounts before 14 days; the individual tissues could be pooled for analysis only after 16 days. Lipoprotein lipase activity in the three fat tissues was 40–50% lower in 20-, 24-, and 30-day-old rats than in adults.

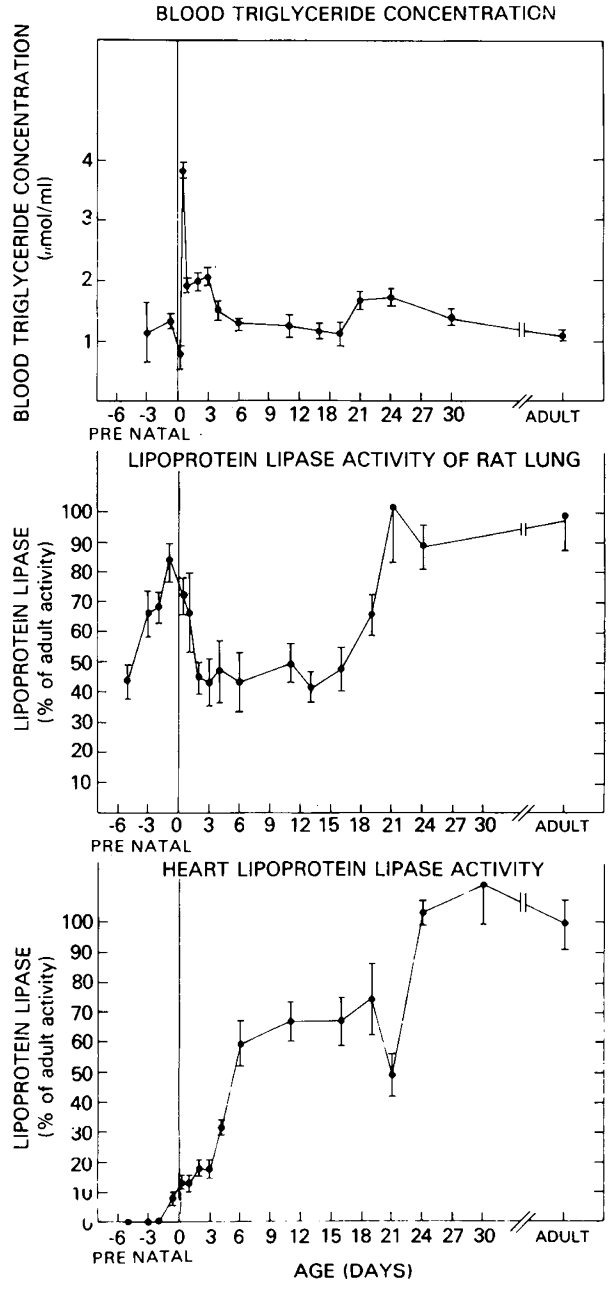

Fig. 3. Blood triglyceride concentration and lipoprotein lipase activity in lung and heart of developing rats. Lipoprotein lipase activity is expressed as percent of adult activity and was calculated as units per gram wet weight; 1 U = 1 μmol triglyceride hydrolyzed per hr at 37°. Lipoprotein lipase activity in the lung of adult rats was 7–11 U/g; enzyme activity in heart was 25–40 U/g. There were 6–10 animals in each group.

The marked rise in blood triglyceride levels immediately after birth coincides with the onset of suckling which in the rat starts almost at birth. Indeed, examination of the stomachs of all rats showed that they were full of milk as early as 30 min after birth. The triglyceridemia that starts in the immediate postnatal period and lasts for several days probably results from the combination of high fat intake [rat milk contains 10–12% fat (14, 21), almost exclusively in the form of long chain triglycerides (21)] and low clearing ability of the extrahepatic tissues (Fig. 3).

DISCUSSION

A sudden change from the high carbohydrate diet of the fetus to the high fat diet of the newborn occurs at birth. The high fat content of milk is probably responsible for the elevation of lipid levels in the blood immediately after birth (Fig. 3) (24), inasmuch as lipid digestion (21) and absorption (25) are well developed in the newborn rat. A major constituent of blood lipids are the triglycerides transported in the form of chylomicrons and very low density lipoproteins (29, 33). Chylomicrons, formed in the intestinal mucosa during fat absorption, and very low density lipoproteins synthesized in the liver cannot cross the capillary endothelium in most extrahepatic tissues (33). Circulating triglycerides are hydrolyzed to free fatty acids in the capillary endothelium by the enzyme lipoprotein lipase (29, 33). The enzyme is found in most tissues that utilize blood triglyceride and activity is proportional to the capacity for removal of triglyceride from the blood (29, 33). The level of lipoprotein lipase activity depends on the physiologic and nutritional state and varies from tissue to tissue. Thus, in adipose tissue lipoprotein lipase activity and triglyceride uptake decrease sharply during fasting (29), diabetes (29), or lactation (17); activity in the lung is unaffected by the nutritional state (18, 19), whereas that in heart increases 2- to 3-fold during fasting (3). The net effect of these changes in lipoprotein lipase activity is the channeling of circulating triglyceride from one tissue to another according to specific needs (during fasting from storage in adipose tissue to heart and lung, in the lactating female to the mammary gland for milk formation).

The high level of blood triglyceride in the newborn is probably the result of inefficient clearing. Adipose tissue is of major importance in clearing circulating triglycerides; it has a relatively high lipoprotein lipase activity and due to its large mass is the major storage site of blood triglyceride (29, 33). Phylogenetically and ontogenetically, adipose tissue is one of the last major tissues to appear. In some mammals including man it develops during the last trimester of gestation (14, 26), whereas in other species such as the rat it does not develop until after birth (14, 26). Indeed, we could not collect sufficient tissue for study from either omentum, epididymal, or parametrial adipose tissue until 16–18 days after birth. The activity in adipose tissue of 20-day-old rats was 40–50% of that in the adult. Brown adipose tissue is present before birth (15) and plays an important role in heat production (23); although it has lipoprotein lipase activity (24), its role in triglyceride clearing is unknown at present.

Heart, which in the adult rat has the highest lipoprotein lipase activity level of all tissues investigated (3, 29), had only traces of activity at birth (Fig. 3); although lung had higher activity in the newborn, the activity rate in this organ (18, 19) is much lower than that in heart (3, 29) and could not contribute significantly to the clearing of circulating triglyceride. Indeed, our data show an inverse relationship between heart lipoprotein lipase activity and blood triglyceride concentration; blood triglyceride levels were high during the first 3 days after birth and during weaning when the activity in heart was low (Fig. 3).

One can assume, therefore, that the premature infant of less than 30–32 weeks of gestation resembles the newborn rat in the complete lack of fat depots (14, 26) and thus of markedly reduced triglyceride clearing ability. Indeed, the lower the gestational age of the premature infant, the greater the impairment in triglyceride clearing (1).

In addition to the role of lipoprotein lipase in clearing circulating triglyceride, the enzyme may have a special function in the growth and maturation of individual organs. The marked difference in the developmental profile of lipoprotein lipase in heart and lung (Fig. 3) could be related to the degree of maturation of these organs immediately before and after birth.

The complete lack of heart lipoprotein lipase activity during late fetal development and its very low activity in the newborn are probably related to the fact that, in the rat, the final differentiation of this organ occurs during the first 3 weeks after birth (31, 34). The rapid rise of enzyme activity after birth could be related to the high fat content of the diet; it was shown that the activity level in adult heart increased several fold after feeding a fat rich diet (27). The sharp fall in enzyme activity from 73 to 48% of adult activity at weaning (Fig. 3) could also be related to dietary effects, namely, the transition from a high fat diet to rat Purina chow—a high carbohydrate diet. Low lipoprotein lipase activity in the perinatal period would indicate that the heart is unable to use circulating triglyceride-fatty acids immediately before and after birth.

A completely different developmental pattern is seen in the lung. Although in the mature rat lipoprotein lipase activity is much lower in the lung (18, 19) than in heart (3, 29), it reaches 70% of adult activity 3 days before birth (Fig. 3). Functional maturity of the lung (6) is essential for survival of the newborn (2). Lung maturation occurs towards the end of gestation (4, 10) and is directly related to the synthesis and storage of surfactant, a complex phospholipid that lines the alveoli (10). Long chain fatty acids are essential for the synthesis of dipalmitoyl phosphatidylcholine, the chief component of lung surfactant. The main source of fatty acids for lung metabolism are plasma fatty acids (10); however, the relative contribution of free fatty acids vs. triglyceride-fatty acids to lung metabolism and surfactant synthesis is unknown. The presence of lipoprotein lipase activity in the lung indicates that the lung is able to remove triglyceride-fatty acids from the circulation (18); subsequent studies with isolated perfused lungs showed that triglyceride-fatty acids are precursors of lung phospholipids (20).

The activity level of other pathways leading to fatty acid accumulation in the lung is also higher during late fetal development and coincides with the surge in surfactant synthesis. In the rabbit, *de novo* synthesis of long chain fatty acids from acetate reaches adult levels in the 23-day-old fetus (gestation in the rabbit is 31 days) (11). Lipid biosynthesis from glucose is higher in fetal than in adult rabbit lung (22); furthermore, in the fetal lung a large part (60%) of glucose carbon atoms channeled into lipid are incorporated into fatty acids (22), whereas at all other ages, glucose is chiefly a precursor of lipid glycerol, and only a small amount (10–15%) is incorporated into glyceride-fatty acids.

The present study shows that lipoprotein lipase activity is high in the fetal lung during the period of marked surfactant synthesis; the activities of choline kinase and choline phosphotransferase, enzymes involved in phospholipid synthesis, are also highest during this period (9, 10). At birth, when an adequate reserve of surfactant is present, the activity of lipoprotein lipase decreased sharply (Fig. 3) as did other enzymes involved in lung phospholipid synthesis (9, 10).

Surfactant synthesis and lung maturation can be accelerated by the administration of corticosteroids; these hormones have been shown to stimulate the activity of choline kinase and choline phosphotransferase (9) as well as the activity of lipoprotein lipase in the lung (19). The high lipoprotein lipase activity during the period of marked surfactant synthesis suggests that the fetal lung utilizes circulating triglyceride-fatty acids for surfactant synthesis.

CONCLUSION

Lipoprotein lipase activity was studied from the late fetal period throughout development in the rat. Enzyme activity in acetone powders of heart, lung, and adipose tissue was tested with doubly labeled ([^{14}C]palmitate, [^{3}H]glyceryl) triglyceride substrate. Blood triglyceride levels were measured at all ages studied.

Lipoprotein lipase activity was absent in the heart until 5 hr before birth; it increased gradually after birth from 7.8% of adult

activity to 17% at 3 days, 59% at 8 days, and 73% at 15 days; activity dropped sharply from 75 to 49% of adult activity at weaning (day 21); adult activity levels were reached at 24 days.

In the lung, lipoprotein lipase activity was high in the fetus: 70% and 84% of adult activity at 3 and 1 day before birth, respectively; it decreased to 45% of adult activity at 2 days of age and remained at that level until 15 days; adult activity was reached at 21 days.

Lipoprotein lipase in adipose tissue could be tested only after 15 days. The activity was 40–50% lower in 20-, 24-, and 30-day-old rats than in adults.

Blood triglyceride concentration increased sharply from 0.7 ± 0.2 μmol/ml at birth to 3.85 ± 0.25 μmol/ml 2–10 hr after birth, remained elevated (2.0 μmol/ml) for the first 3 days after birth, and decreased afterward to 1.2 μmol/ml.

The data indicate that the triglyceridemia of the postnatal period is related to low clearing ability of the extrahepatic tissues and to the high fat intake. The high lipoprotein lipase activity in fetal lung suggests that circulating triglyceride-fatty acids could be utilized for surfactant synthesis.

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