Relation Between Endogenous Lipoprotein Lipase Activity, Free Fatty Acids, and Glucose in Plasma of Women in Labour and of their Newborns

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Changes in the plasma levels of glucose and free fatty acids during and after birth have been investigated by several workers (Van Duyne and Havel, 1959; Novak *et al.*, 1961; Chen *et al.*, 1965; Keele and Kay, 1966). Compared to cord blood levels, the plasma free fatty acid levels rose at about the second hour after birth, and the glucose level fell. Inasmuch as hypoglycaemia was a concomitant finding at this time, many workers felt it was the main factor leading to increased levels of free fatty acids in the plasma of the newborn (Novak *et al.*, 1961; Högstädt and Lindquist, 1963; Melichar, Novák, and Koldovský, 1964; Chen *et al.*, 1965; Keele and Kay, 1966).

The purpose of this study was to investigate the relation between endogenous lipoprotein lipase activity, plasma glucose, and free fatty acid levels in the first few hours after birth.

Material and Methods

The study was carried out on 21 mothers and their 21 newborn babies. All babies were born after an uneventful pregnancy and an uncomplicated delivery. The mean birthweight of the infants was 3.34 kg. Data were obtained from 9 healthy adult females for comparison.

Blood samples were collected from the cubital vein during the last stage of labour, from the cord immediately after birth; and from the newborn infants by the use of a polyethylene catheter inserted into the umbilical vein during the third hour (between 120 and 180 minutes) after birth. Heparinized syringes were used for the collection of all blood samples. A fraction of the blood sample from each subject was transferred to tubes kept in an ice-bath and taken thus to the laboratory for determination of free fatty acids. The remaining blood fractions were transferred to test-tubes at room temperature and taken to a 37°C. incubator within 15 minutes of collection. All mothers were in a fasting state (mean 14 hours) at the time blood was taken and

none had received any parenteral solutions before or during labour.

The newborn babies were divided into two groups. Group I, 10 babies that were kept in a fasting state during the study period. Group II, 11 babies that were fed glucose water (glucose 50 g./m.²), given in three 30-minute intervals during the first 90 minutes after birth.

Free fatty acids in plasma were determined by the Dole method, as modified by Burns (Dole and Meinertz, 1960; Burns *et al.*, 1963) on paired samples. The analytical precision in duplicate determinations was 0.002 mEq/l.

Endogenous lipoprotein lipase activity was expressed as the amount of free fatty acids, in mEq/l., produced by 1 ml. plasma after 60 minutes' incubation at 37°C. The incubation mixture was prepared according to the Kern method (Kern, Steinmann, and Sanders, 1961). The substrate solution was kept at 37°C. for 30 minutes before the addition of plasma samples. A separate control solution (1 ml. plasma at 37°C. for 3 minutes) was used for each sample. After incubation, the free fatty acids were extracted by the same method (Dole and Meinertz, 1960; Burns *et al.*, 1963), and again the analytical precision in paired samples was 0.002 mEq/l.

Blood glucose was determined by the Somogyi method. The analytical precision in duplicate samples was 1.1 mg./100 ml.

Results

Results are shown in the Table and Figure.

Mean blood glucose level in the mothers' blood during labour was 95 ± 12.4 mg./100 ml.; in cord blood this value was 89 ± 18.3 mg./100 ml. and in the newborns in the first group (those kept in the fasting state), 60.7 ± 12.4 mg./100 ml. Mean glucose levels in the second group of newborns (those who were fed glucose) was 142 ± 49.4 mg./100 ml. in the third hour after birth. The blood glucose levels in the two groups of newborns were significantly different from one another.

Mean free fatty acid in maternal blood was

TABLE

Free Fatty Acids, Lipoprotein Lipase Activity, and Blood Glucose in Maternal Blood, Cord Blood, and in Blood of Newborns in Third Hour of Delivery

Case No.	Infant Birth-weight (g.)	Time (hr.) of Mothers' Fasting	Plasma Free Fatty Acids (mEq/l.)			Plasma Lipoprotein Lipase Activity (units)			Blood Glucose mg./100ml.		
			Mothers	Cord Blood	Newborns (3 hours after birth)	Mothers	Cord Blood	Newborns (3 hours after birth)	Mothers	Cord Blood	Newborns (3 hours after birth)
1	2700	6.5	0.580	0.250	0.892	0.192	0.210	0.584	80	—	—
2	4000	16	0.615	0.390	0.846	—	0.610	—	94	71	60
3	3100	16	0.862	0.310	—	1.498	0.690	—	115	100	—
4	2900	15	0.800	0.240	0.880	1.050	0.660	0.780	92	71	58
5	3350	15	0.820	0.214	0.892	1.250	0.632	1.338	96	80	51
6	3300	15.5	0.787	0.242	0.930	0.113	0.158	0.170	100	83	65
7	2600	16.5	0.552	0.210	0.868	0.190	0.290	0.395	97	75	55
8	3800	15	0.526	0.315	0.947	0.420	0.158	0.313	97	75	65
9	3050	16.5	0.764	0.235	0.852	0.394	0.415	—	107	80	68
10	3310	14	0.605	0.342	0.868	0.120	0.208	0.332	102	70	55
11	3350	6	0.583	0.444	0.722	0.280	0.100	0.500	81	76	61
12*	3900	15	0.500	0.222	—	0.166	0.289	—	81	78	—
13*	4250	16	0.736	0.290	—	0.264	0.315	—	68	51	—
14*	4650	14	0.610	0.333	0.555	0.240	0.269	0.273	102	73	116
15*	3800	14	0.648	0.135	0.300	0.209	0.465	0.470	86	75	113
16*	3600	14	0.684	0.263	0.421	0.144	0.308	0.293	107	61	260
17*	3200	6	0.777	0.305	0.444	0.165	0.266	0.270	90	60	118
18*	2800	12	0.617	0.323	0.590	0.193	0.217	0.220	76	71	155
19*	3000	14	0.558	0.294	0.500	0.144	0.193	0.202	92	71	120
20*	3500	13	0.470	0.352	0.647	0.187	0.162	0.180	110	60	125
21*	3600	12	0.571	0.235	0.571	0.143	0.395	0.400	107	86	130

*Received glucose orally 50 g./m.²

0.651 $\pm$ 0.362 mEq/l. and high compared to the control levels in our group of 9 adult females, mean 0.482 $\pm$ 0.151 mEq/l. In cord blood this value was much lower (0.304 $\pm$ 0.267 mEq/l.). A significant rise was observed in the free fatty acid levels in the newborns in Group I in the first 2–3 hours of life, from a mean of 0.283 to a mean of 0.870 mEq/l. In infants in Group II, free fatty acids also showed a rise, the mean value two hours after birth being 0.503 mEq/l. Though this value was high compared to cord blood free fatty acids, it was significantly lower than the values obtained on Group I infants.

Mean endogenous lipoprotein lipase activity in maternal blood was 0.371 $\pm$ 0.392/60 min. per ml; in cord blood, 0.365 $\pm$ 0.219; and in the newborns in Group I, 0.588 $\pm$ 0.372 at the third hour after birth. In the control group, the mean value of lipoprotein lipase activity was 0.264 $\pm$ 121. Though maternal and cord blood were essentially comparable in lipase activity, the enzyme activity in this group of newborns showed a significant rise in the first few hours after birth. Lipoprotein lipase activity did not show any rise in the infants in Group II and remained in the same range

(0.288 $\pm$ 0.121) as that found in maternal blood and in cord blood. A significant difference was established in enzyme activity between the two groups of infants.

Comments

A rise in plasma free fatty acids and lipids in the first few hours after birth is an established fact (Rafstedt, 1955; Van Duyne and Havel, 1959). The rise in plasma free fatty acids starts 30 minutes after birth, reaching a peak in the second hour and continuing at this peak until the end of the first month (Persson and Gentz, 1966). Concomitantly the blood glucose falls significantly below cord blood levels. Various hormonal, neural, and enzymatic effects have been suggested as causing this hypoglycaemia in the newborn period. Hypoglycaemia or defective utilization of glucose by the cells is considered to lead, directly or indirectly, to raised free fatty acid levels in the newborn (Bragdon and Havel, 1954; Dole, 1956; Gordon and Cherkas, 1956; Bierman, Schwartz, and Dole, 1957; Driscoll and Hsia, 1958; Goodman and Gordon, 1958; Laurell and Christensson, 1958; Cornblath *et al.*, 1965; Stimmler, Brazie, and O'Brien, 1963; Baird

FIG.—Glucose, free fatty acid, and plasma lipoprotein lipase activity in blood of 21 mothers, 21 cord bloods; 10* Group I (fasted) newborns at 3 hours; and 11* Group II (glucose-fed) newborns at 3 hours. Values for 9 adult controls are also shown. Mean $\pm$ 1 SD given.

Statistical relationships:

Glucose	Probability	FFA	Probability	Lipoprotein Lipase	Probability
Mother vs cord	$p < 0.001$	Mother vs cord	$p < 0.001$	Mother vs cord	Insignificant
Cord vs newborn (fasted)	$p < 0.001$	Cord vs newborn (fasted)	$p < 0.001$	Cord vs newborn (fasted)	$p < 0.025$
Mother vs newborn (fasted)	$p < 0.001$	Cord vs newborn (glucose-fed)	$p < 0.001$	Cord vs newborn	$p < 0.30$
		Mother vs newborn (fasted)	$p < 0.001$	Newborn (fasted) vs newborn (glucose-fed)	$p < 0.05$
		Newborn (fasted) vs newborn (glucose-fed)	$p < 0.001$		
		Controls vs mother	$p < 0.10$	Controls vs mother	$p < 0.30$

*Not all these two groups of newborns were sampled at 3 hours (see Table), hence the numbers of points shown in the Figure for these two groups do not necessarily total 10 and 11, respectively.

and Farquhar, 1962; Nestel, 1964; Shelley, 1964; Glick *et al.*, 1965; Melichar *et al.*, 1965; Gerlini, Sbraccia, and Gerlini, 1966).

In this series of infants, comparison of free fatty acid levels in Group I infants (who were not fed glucose after birth) with those in Group II (who

were glucose-fed in the first 90 minutes) showed that free fatty acids were significantly raised in Group I infants, indicating clearly the effect of glycaemia on free fatty acid level. Except for blood glucose levels, the two groups of newborns were comparable in all respects.

Hypoglycaemia after an insulin load leads to an immediate increase in growth hormone (HGH) secretion in the adult. Acute starvation and exercise have a similar effect (Glick *et al.*, 1965). A correlation between plasma glucose levels and plasma HGH concentrations could not be established in the newborn (Cornblath *et al.*, 1965). However, the administration of insulin, even in the first few hours after birth, resulted in an increase in HGH levels. It is known that hyperglycaemia also causes a rise in HGH levels in the first 10 days of life. It has been suggested that the newborn reaction to hypo- or hyperglycaemia differs from that shown by the adult (Cornblath *et al.*, 1965). Laron *et al.* (1967) reported a manyfold increase in HGH levels of the newborn, compared to cord blood levels, occurring a few hours after birth. Hypoglycaemia was suggested as at least partly responsible for this increase. Laron *et al.* also reported a significant increase in FFA after birth. It has been shown that HGH leads to release of FFA, whereas the administration of glucose plus insulin or feedings suppressed this rise (Glick *et al.*, 1965; Raben and Hollenberg, 1959).

The enzyme system effective in lipolytic processes is the lipases. The demonstration of a clearing factor which becomes active after the injection of heparin has led to many studies and a better knowledge of the characteristics of lipoprotein lipases (Hahn, 1943; Bragdon and Havel, 1954; Engelberg, 1958a; Sailer, Sandhofer, and Braunsteiner, 1961; Geday, 1966). However, the presence of a spontaneous or endogenous lipoprotein lipase and its role in the breakdown of triglycerides in the chylomicra under normal conditions is still controversial. Some authors think that there is no lipoprotein activity in the plasma before exogenous heparin (Högstedt and Lindquist, 1963). Others, as a result of observations carried out in animals and humans, report the presence of an endogenous lipase similar to lipoprotein lipase produced after heparin (Jeffries, 1954a, b; Robinson, Jeffries, and French, 1954; Engelberg 1955, 1956, 1957, 1958b; Cseh and Szabo, 1963; Sandhofer, Sailer, and Braunsteiner, 1964; Sailer, Sandhofer, and Braunsteiner, 1965; Geday, 1966). The results obtained in this series of newborn infants appear to support the latter view.

Lipoprotein lipase activity has been reported to be low in pregnant women, in that the administration of heparin to pregnant women has not resulted in an increase in lipase activity (Sandhofer, Sailer, and Braunsteiner, 1961; Auerswald *et al.*,

1965). In our group of pregnant women, endogenous lipoprotein lipase activity was found to be comparable to that of the control group.

Endogenous lipoprotein lipase activity in cord blood was also in the same range as that of the normal controls, and comparable to values obtained on the mothers. Blood taken from the newborn infants in Group I at the third hour after birth showed a significant rise in endogenous lipoprotein lipase activity compared to maternal and cord blood levels ($p < 0.025$). Due to differences in methodology, it has not been possible to compare the absolute values obtained with those reported elsewhere. FFA levels were also found to be significantly increased at this time.

In the immediate newborn period, hypoglycaemia appears to be one of the main factors inducing a rise in free fatty acids. As stated above, a significant fall was noted in blood glucose levels in infants in Group I. On the other hand, the group of newborns in which blood glucose levels were raised by feeding glucose did not show a significant rise in their plasma FFA levels. Lipoprotein lipase activity in this group remained at the maternal and cord blood levels. These findings underline the important role of blood sugar levels on endogenous lipoprotein lipase activity, and also suggest that the rise in free fatty acids is probably due to endogenous lipoprotein lipase activity.

Another finding of interest was the increase in free fatty acids observed in infants in Group II. Plasma endogenous lipoprotein lipase activity remained at cord blood levels in this group. Though the increase in free fatty acids was not as great as that noted in Group I infants, the occurrence of a rise, however small, may indicate that tissue lipase activity is independent of plasma lipoprotein lipases.

HGH levels were not determined in this series of infants, and therefore our data provide no direct evidence for the view that hypoglycaemia in the newborn induces a release in HGH, thereby causing an increase in lipoprotein lipase activity. However, the relation observed among plasma glucose levels, HGH secretion, and plasma free fatty acids provides circumstantial evidence supporting the view that endogenous lipoprotein lipase activity acts as a link in these relationships.

Summary

Free fatty acids, glucose, and lipoprotein lipase activity were determined in the plasma of healthy pregnant women in the last stage of labour, in cord blood, and in the plasma of the newborns. One group of newborns was left fasting and a

second group was fed glucose (50 g./m.²) during the first 90 minutes after birth.

Endogenous lipoprotein lipase activity determined in the third hour after birth was significantly raised in the fasted group of newborns. The rise in free fatty acid levels was also more striking in the fasted group.

The findings supported the view that hypoglycaemia, directly or through the action of HGH, acts as the basic mechanism in the production of active endogenous lipoprotein lipase, and in the release of free fatty acids in the immediate neonatal period.

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