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INHIBITORY EFFECT OF GLUCOSE ON THE MATURATION OF RAT LIVER MITOCHONDRIA AT BIRTH

PHOSPHOLIPID AND OXIDATIVE METABOLISM

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(1) The rate of ATP synthesis coupled with succinate oxidation in rat liver mitochondria is low at birth and increases rapidly during the first postnatal hours (Nakazawa, T., Asami, K., Suzuki, H. and Yakawa, O. (1973) J. Biochem. 73, 397–406). A glucose injection given to newborn rats immediately after birth seemed to delay this maturation process. (2) Glucose administration specifically diminished the rate of $^{32}P_i$ incorporation into phosphatidylcholine both in microsomes and in mitochondria while other phospholipids remained unaffected. (3) In newborn rat liver, $^{32}P_i$ incorporation into phospholipids can be explained by de novo synthesis of phospholipids in microsomes followed by transfer to mitochondria with two exceptions: phosphatidylserine and sphingomyelin. Indeed, after a 20-min incorporation of $^{32}P_i$ into phospholipids, the specific radioactivity of phosphatidylserine and sphingomyelin was higher in mitochondria than in microsomes. (4) As far as phospholipid synthesis is concerned, no precursor-product relationship could be observed between light and heavy mitochondria.

Introduction

At birth, rat liver mitochondria have a low rate of ATP synthesis coupled with substrate oxidation [1,2], that is to say a lack of efficiency in oxidative phosphorylation. This efficiency improves rapidly during the postnatal hours [3]. The fast mechanisms by which immature mitochondria shift to functional ones are not fully understood. It is known that the mitochondrial content of adenine nucleotides increases at birth concomitantly with the respiratory activity [4]. This improvement in the capacity of ATP synthesis through the oxidative phosphorylation machinery is one of the early events occurring in rat mitochondria at birth. During the maturation occurring from birth to adulthood an active synthesis of new mitochondria takes place, owing to the increase in both the liver mass and its mitochondrial content [5]. Moreover, the specific activity of several mitochondrial enzymes will continue to increase during several weeks after birth but a respiratory control similar to that of the adult is reached within a few hours. Sandor and Pollak [6] reported that the increased respiratory control which occurs within the first hours after birth appears not to be dependent on cycloheximide-sensitive protein synthesis occurring on cytoplasmic ribosomes. We have therefore investigated the possibility of a change occurring in phospholipid biosynthesis.

The gross distribution of the main phospholipids of liver mitochondria does not appear different in the newborn and in the adult rat [7]; their fatty acid pattern is hardly modified [8] or not affected [9] between birth and the first postnatal weeks. However, Hostetler et al. [10] report levels

of phosphatidylserine, a minor phospholipid in liver mitochondria, 1 day before birth significantly higher than those in the adult (4.4 vs. 1.3%). Besides, it is obvious that variations in phospholipid metabolism can be better elucidated by radioisotopic methods than by quantitation [11,12]. Therefore, we have used $^{32}P_i$ which can be incorporated into all phospholipids, especially since incorporation into mitochondrial and microsomal fractions appeared faster in the newborn than in the adult [7]. However, it is not known whether this incorporation is only related to the increase in liver mass, or if it is linked to maturation of the mitochondria.

A glucose injection was shown to induce a repressive effect, mainly on protein synthesis in the adult [13] and in the newborn [14]. At birth, a glucose administration was shown to inhibit enzymes of glycogenolysis [15] and neoglucogenesis [16] as well as ornithine transcarbamylase, a mitochondrial enzyme [17].

In the present work, glucose administration at birth was used to perturb the natural processes and the effect of glucose on the respiratory activity and $^{32}P_i$ incorporation into the phospholipids of heavy and light mitochondria were studied after injection of $^{32}P_i$ in vivo.

Material and Methods

Animal treatments

Female Wistar rats were caged overnight with males and fertilization was confirmed by vaginal smear. Gestation lasts 21.5–22 days in this strain. Pregnant rats were killed by decapitation on the morning of the 22th day. Fetuses were delivered, the umbilical cord tied and cut, and each newborn received intraperitoneally either 50 µl of 0.5 g/ml glucose solution per 5 g animal or an equivalent volume of 0.9% NaCl. Newborn rats were held in a humidicrib at 37°C without feeding. When adults were studied, male Wistar rats fed ad libitum were injected intraperitoneally with 4 ml of either NaCl or glucose solution per 400 g animal weight and killed 2 h later.

For polarographic analysis, the newborn rats were killed immediately after birth or 2 or 4 h later. For lipid analysis, 70 min after the death of the female, newborns were injected with carrier-free $^{32}P_i$ (150–200 µCi/25 µl per 5 g animal) supplied by the Commissariat à l'Energie Atomique, France. They were killed 90 min after the death of the female and the liver quickly removed.

Preparation of mitochondria and microsomes

All operations were carried out at 0–4°C.

For lipid analysis, the livers of three animals were pooled (about 1 g liver), minced, rinsed to remove blood and homogenized in 9 ml isolation medium/g wet weight (250 mM sucrose, 0.1 mM EDTA, 3 mM Tris-HCl, pH 7.4) using three up and down strokes of a hand-driven Teflon pestle in a 5 ml glass potter. The homogenate was centrifuged for 10 min at $500 \times g$. The supernatant was then centrifuged for 10 min at $800 \times g$ to pellet 'heavy mitochondria'. The $800 \times g$ supernatant was centrifuged for 10 min at $8000 \times g$ to pellet 'light mitochondria'. The supernatant was centrifuged for 10 min at $20000 \times g$. This intermediate pellet was discarded and the supernatant centrifuged again at $100000 \times g$ for 60 min to obtain the microsomal fraction. Heavy and light mitochondria were suspended separately in 5 ml of KCl buffer/g liver weight (130 mM KCl, 3 mM Tris-HCl, pH 7.4) and centrifuged for 10 min at $8000 \times g$

For respiratory measurements a larger amount of mitochondria was needed. The livers from 10–12 animals were pooled and mitochondria were routinely prepared as described by Aprille and Asimakis [18]. With this technique, both heavy and light mitochondria were pooled together. Proteins were estimated by the biuret method using bovin serum albumin (fraction V, Sigma Chemical Co.) as a standard [19].

Analytical procedures

For phospholipid analysis, the mitochondrial and microsomal pellets were collected and extracted with chloroform/methanol (2 : 1) [20], then analyzed by two-dimensional thin-layer chromatography as previously described [21]. The specific radioactivity of inorganic phosphorus was measured according to the method of Lindberg and Ernster [22]. Calculations are given for 100 µCi $^{32}P_i$ injected per animal.

Respiratory activity was assayed polarographically using a vibrating platinum electrode in a

water-jacketed cell maintained at 30°C (oxygraph KM, Gilson Medical Electronics).

The assay medium consisted of 225 mM sucrose, 10 mM KCl, 10 mM KH_2PO_4/K_2HPO_4, 5 mM $MgCl_2$, 1 mM EDTA, 10 mM succinate and 10 mM Tris-HCl, pH 7.4 (2 ml final volume). Following addition of 1.4–1.9 mg mitochondrial proteins, State 3 respiration [23] was initiated by the addition of 160 nmol ADP.

Results

Delay in the increase in respiratory activity of liver mitochondria during the post-natal hours induced by glucose administration at birth

Fig. 1 shows that the respiratory control ratio increased from 2 to 3.8 when liver mitochondria were prepared from newborn rats immediately (A), 2 h (B) or 4 h (C) after birth. Although the rate of succinate oxidation in the absence of ADP (State 4) varied somewhat from one experiment to the other, the increase in the respiratory control ratio was always observed in five experiments (increase ranging from 40 to 80% 2 h after birth and 60 to 110% 4 h after birth). This is in agreement with previous reports [4,18]. If, immediately after birth, glucose was injected into rats and their mitochondria prepared 2 h later, the respiratory control ratio did not seem to be increased or was even uncoupled when compared to the mitochondria prepared immediately after birth. The rate was sometimes even lower: Fig. 1D shows a typical experiment which has been reproduced five times. The average respiratory control ratios were 1.9 ± 0.2 immediately after birth, 3.2 ± 0.2 if the mitochondria were prepared from rats killed 2 h after birth and 1.6 ± 0.2 if the newborn rats were treated with glucose and killed 2 h later. When the mitochondria were prepared 4 h after glucose administration, they were almost as well coupled (Fig. 1E) as those prepared from the control animals (Fig. 1C). A glucose injection into adult rats had no effect on the respiratory control ratio of liver mitochondria prepared and tested under the same conditions as for the newborn. (respiratory control ratio 4.8 ± 0.3 vs. 4.9 ± 0.3, respectively, for control and glucose-treated rats in three different experiments).

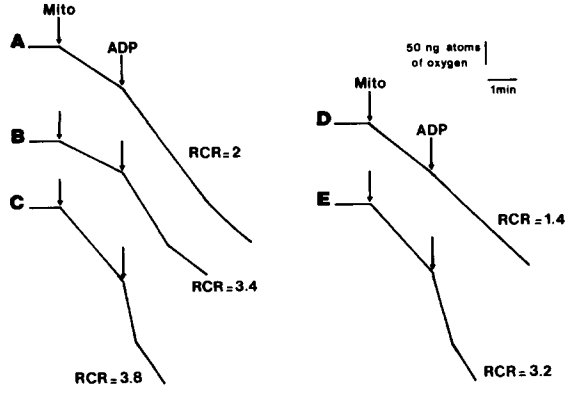

Fig. 1. Polarographic traces of the respiratory activity of rat liver mitochondria isolated from: (A) newborn, (B) 2-h-old, and (C) 4-h-old rats, as compared to mitochondria isolated from rats injected with glucose at birth and killed after (D) 2 h, and (E) 4 h of postnatal life. Experimental conditions are described in Material and Methods. Mito, mitochondria; RCR, respiratory control ratio.

Influence of glucose administration on $^{32}P_i$ incorporation into mitochondrial and microsomal phospholipids of newborn rat liver

In Table I, the distribution of phospholipids in heavy and light mitochondria has been studied and compared to that of the microsomal fraction. The percentages of the various lipids found in light mitochondria were always intermediate between those of heavy mitochondria and those of microsomes. This perhaps means that light mitochondria represent a mixture of heavy mitochondria and microsomes. Considering that microsomes are devoided of diphosphatidylglycerol, that light mitochondria are a mixture of heavy mitochondria and microsomes and making the assumption that heavy mitochondria are microsome free, the contamination of light mitochondria by microsomes would be 35%.

When $^{32}P_i$ was injected 90 min after birth, and the rats killed 20 min later, the specific radioactivity of total phospholipids was about 1.5-times higher in microsomes than in heavy mitochondria (Table II). $^{32}P_i$ incorporation in total phospholipids was slightly higher in light mitochondria than in heavy mitochondria, as could be expected from the results presented in Table I. The administration of glucose to rats immediately after birth apparently did not modify $^{32}P_i$ incorporation into

TABLE I

PHOSPHOLIPID COMPOSITION OF LIVER MITOCHONDRIA AND MICROSOMES FROM 90-min-OLD RATS

Values are given in percentage of total lipid phosphorus. Mean ± S.E., four experiments for heavy and light mitochondria, three for microsomes. An average value of 0.2% for the phosphatidic acid content of all fractions will be used for further calculations, since this content was too low to be estimated more accurately.

	Heavy mitochondria	Light mitochondria	Microsomes
Sphingomyelin	2.0 ±0.6	3.2±0.1	9.15±0.7
Phosphatidylcholine	46.5 ±1	50.8±0.2	55.3 ±0.9
Phosphatidylserine	1.8 ±0.2	3.0±0.4	5.35±0.2
Phosphatidylinositol	6.02±0.2	7.8±0.2	8.63±0.5
Phosphatidylethanolamine	29.6±0.8	25.7±0.4	21.5 ±0.3
Diphosphatidylglycerol	13.3 ±0.9	8.6±0.7	0

TABLE II

SPECIFIC RADIOACTIVITY (SRA) OF TOTAL PHOSPHOLIPIDS OF HEAVY AND LIGHT MITOCHONDRIA AND MICROSOMES, 20 min AFTER $^{32}P_i$ INJECTION IN VIVO

Each newborn was injected at birth with glucose or NaCl (control) and was killed 90 min later, as described in Material and Methods. Specific radioactivities are expressed in cpm/μg phosphorus (mean of two experiments). Specific radioactivity of liver P_i was 38 124 and 41 913 cpm/μg phosphorus in control and glucose-treated animals, respectively.

	Heavy mitochondria		Light mitochondria		Microsomes	
	Control	Glucose	Control	Glucose	Control	Glucose
SRA lipid P	351	360	414	409	522	565
SRA lipid P ($\times 10^3$)/SRA P_i	9.3	8.8	11	9.9	13.9	13.6

TABLE III

SPECIFIC RADIOACTIVITY OF THE INDIVIDUAL PHOSPHOLIPIDS (SEE LEGEND TO TABLE II)

	Heavy mitochondria		Light mitochondria		Microsomes	
	Control	Glucose	Control	Glucose	Control	Glucose
Sphingomyelin	103	104	52	51.1	30.4	38.9
Phosphatidylcholine	133	105	145	120	198	158
Phosphatidylserine	242	242	83.5	86.6	66.6	88.1
Phosphatidylinositol	728	781	693	817	855	919
Phosphatidylethanolamine	364	397	471	586	901	1010
Diphosphatidylglycerol	75.5	53.3	78.1	74.6	0	0
Phosphatidic acid [a]	59000	64000	52000	55000	70000	85000

[a] See legend to Table I.

phospholipids. Glucose administration did not change the entry of $^{32}P_i$ into the liver pool of P_i either, since the specific radioactivity of $^{32}P_i$ was not modified.

The specific radioactivity of the individual phospholipids is listed in Table III. The incorporation of $^{32}P_i$ into phosphatidic acid and phosphatidylinositol was similar in the three subcellular fractions. The fact that animals were killed only 20 min after $^{32}P_i$ injection explains the high specific

radioactivity of phosphatidic acid. The radioactivity of phosphatidylethanolamine and phosphatidylcholine was higher in microsomes than in the two mitochondrial fractions. The incorporation of $^{32}P_i$ in diphosphatidylglycerol, which is located only in mitochondria [24], was not different in heavy and light fractions. In contrast, the specific radioactivity of phosphatidylserine and sphingomyelin, which are abundant in microsomes, was about 2.5-fold higher in heavy mitochondria than in light mitochondria or microsomes.

When newborn rats were treated with glucose at birth, $^{32}P_i$ incorporation into phosphatidylcholine was similarly lowered in the three subcellular fractions. $^{32}P_i$ incorporation into phosphatidylethanolamine was slightly enhanced by glucose injection while the modifications observed with other phospholipids did not seem to occur simultaneously in the different fractions (Table III). This effect of glucose was studied further and the results are presented in Table IV. In each experiment, rats from the same litter were divided in two groups. At birth, the first group received a glucose injection, the second one an NaCl injection and all rats were injected with $^{32}P_i$ as previously described. The specific radioactivity of individual phospholipids was determined in mitochondria and microsomes for each group. The ratio of the specificity radioactivity of control animals to that of glucose-treated animals was calculated for each experiment. Table IV presents the mean of the ratios (±S.E.) obtained in six such experiments. Statistical significance was calculated on the differences between the specific radioactivity of each phospholipid in control and glucose-treated animals. Glucose injection induced a significant decrease in $^{32}P_i$ incorporation only in the case of phosphatidylcholine ($P < 0.02$).

TABLE IV

RATIO OF THE SPECIFIC RADIOACTIVITY OF EACH PHOSPHOLIPID IN CONTROL ANIMALS TO THE RADIOACTIVITY OF THE SAME PHOSPHOLIPID IN GLUCOSE-TREATED ANIMALS

Values are means of six experiments ± S.E.

	Mitochondria	Microsomes
Sphingomyelin	0.98 ± 0.1	0.94 ± 0.2
Phosphatidylcholine	1.38 ± 0.07 [a]	1.37 ± 0.06 [a]
Phosphatidylserine	0.91 ± 0.1	0.90 ± 0.1
Phosphatidylinositol	0.93 ± 0.05	0.92 ± 0.06
Phosphatidylethanolamine	0.98 ± 0.04	1.04 ± 0.07
Diphosphatidylglycerol	1.02 ± 0.13	
Phosphatidic acid	0.93 ± 0.07	0.81 ± 0.07

[a] $P < 0.02$ with the paired Student's t-test applied to the difference between the specific radioactivity of each phospholipid in the control and glucose-treated animals.

Discussion

During the perinatal period, Hallman and Kankare [25] have observed changes of the mean density of mitochondria by sedimentation on a continuous density gradient. This density increased during the last days of gestation reaching a maximum at birth, then decreased immediately after birth reaching the adult value 24 h later. this observation, the report of Fleischer et al. [26], and the study of Van Golde et al. [27] using a $1000 \times g$ pellet to prepare mitochondria of optimal purity prompted us to prepare newborn rat mitochondria at $800 \times g$.

The results presented here show that the phospholipid composition of the liver heavy mitochondrial fraction from 90-min-old rats appears similar to that of adult rat liver mitochondria [28]. The diphosphatidylglycerol content, located in the inner mitochondrial membrane [24], agrees with previously reported values (12–13.5% of total phospholipids) for late fetal or newborn rat liver mitochondria [7,10,25,29].

The phospholipid distribution of the light mitochondrial fraction being intermediate between that of heavy mitochondria and microsomes suggests that this light fraction might reflect new mitochondria being synthesized. Discrepancies exist in the literature concerning minor phospholipids. The percentage of phosphatidylserine and sphingomyelin of late fetal rat liver mitochondria amounts to 4.4 and 4.2%, respectively, in Ref. 29 and only trace amounts in Ref. 10. The phosphatidylserine and sphingomyelin contents of adult rat liver mitochondria were identical in the two reports (1.4 and 2.4% [29] or 1.3 and 2.3% [10] of the total phospholipids). The discrepancies be-

tween these reports may be ascribed to the difficulties in obtaining pure newborn rat liver mitochondria. In the present work, the phospholipid composition of light mitochondria could be also explained by a microsomal contamination, eventually due to a functional association.

The phospholipid distribution of heavy and light mitochondrial fractions from newborn rat liver shows the same trends as in the adults, namely a higher diphosphatidylglycerol content in the heavy fraction compared to the light one (10 and 5.5%, respectively) and a lower sphingomyelin content (3.7 and 6.8%). These results have been obtained by Satav et al. [30] and confirmed by our own experiments (not shown).

The specific radioactivity of each phospholipid in the three subcellular fractions (Table III) appears in agreement with de novo synthesis of phospholipids in the endoplasmic reticulum [31], and their transfer to the mitochondria except for phosphatidylserine and sphingomyelin. These phospholipids are present in low amounts in mitochondria, however, the incorporation of $^{32}P_i$ as shown by the specific radioactivity of these two phospholipids was much higher in heavy mitochondria than in microsomes.

In adult rat liver, phosphatidylserine synthesis occurs by base exchange in the endoplasmic reticulum, and it is transferred to mitochondria where it may be decarboxylated to phosphatidylethanolamine [27]. This base-exchange reaction was also shown to be absent in mitochondria from late fetal rat liver in vitro [32]. No pathway for sphingomyelin synthesis has been described in adult or fetal rat mitochondria [27,31]. Moreover, sphingomyelin and phosphatidylcholine are synthesized in the endoplasmic reticulum with the same precursors, phosphocholine and cytidine diphosphocholine. However, they display opposite patterns of $^{32}P_i$ incorporation in the three subcellular fractions. These results reflect the independent turnover of the phosphocholine moiety of sphingomyelin and phosphatidylcholine. This observation extends the previous results already reported in other rat tissues [33].

The specific radioactivity of phosphatidylserine and sphingomyelin is higher in heavy mitochondria than in light mitochondria and in microsomes. This cannot be accounted for by a microsomal contamination and remains to be explained. This result is especially striking for phosphatidylserine. No precursor-product relationship appears between light and heavy mitochondria.

When newborn rats were injected with glucose at birth, a significant decrease in phosphatidylcholine synthesis was observed 90 min later in both mitochondria and microsomes. At the same time, the usual increase in the rate of oxidative phosphorylation was delayed. Mitochondria from glucose-treated animals recovered approximately normal respiratory control values 4 h after birth.

The fact that glucose administration to rats immediately after birth seemed to delay the increase in the respiratory activity of liver mitochondria could be explained in different ways. One possibility would be that, after birth, a processing of some mitochondrial components occurred, this processing being prevented by high levels of glucose. Another possibility would be that the fragility of the mitochondrial membranes was greater in glucose-treated animals than in the controls and that, during the preparation of mitochondria, these mitochondria became more damaged. If glucose administration prevents the processing of some mitochondrial components, the fact that this treatment seemed to delay the normal increase in the respiratory control of mitochondira in a reversible manner can be used as a physiological tool to understand this maturation process.

The glucose injection might modify the endocrine status of the newborn at birth. The day before birth, the insulin/glucagon molar ratio is 16.4 in the fetus, 0.92 in the mother. This ratio falls to 1.00 in the 1-h-old newborn [34]. It is known that glucagon treatment of the adult rat in vivo increases State 3 respiration of liver mitochondria with succinate [35], and that a glucose injection at birth might prevent the increase in plasma glucagon following birth [36]. Although this important result is controversial [37], the insulin/glucagon ratio may be responsible for the mitochondrial maturation at birth, as suggested by Sutton and Pollak [38] and further work in this field would be fruitful.

Finally, it should be remembered that the administration of glucose to hypoglycemic newborn humans, who share several features with the new-

born rat [39], is perhaps not beneficial in all respects.

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