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Lipogenesis *in vivo* in maternal and foetal tissues during late gestation in the rat

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The rate of ^3H_2O incorporation into lipid *in vivo* progressively decreased in liver but increased in parametrial adipose tissue during the last 3 days of gestation. These changes seem to be related to those occurring in plasma insulin and progesterone concentrations during the same period. Foetal liver showed a high rate of lipogenesis, which sharply decreased before parturition. Foetal lung lipogenesis increased during days 20 and 21 of gestation.

During pregnancy, profound metabolic and hormonal changes occur to adapt maternal tissues to foetal growth (Knoop *et al.*, 1973). Very little lipid crosses the rat placenta (Koren & Shafrir, 1964). Maternal carbohydrates are the major energy source for foetal growth. Consequently lipid accounts for the bulk of maternal energy requirements, which results in the increase of plasma lipid during the second phase of gestation (Scow *et al.*, 1964; Knoop *et al.*, 1973). However, plasma lipid decreased just before parturition, suggesting that lipid metabolism is affected by the hormonal changes (Scow *et al.*, 1964; Costrini & Kalkhoff, 1971) that precede parturition. The contribution of lipogenesis *de novo* to these changes may be important (Fain & Scow, 1966), especially in those occurring at the end of gestation. In the present experiments, we have measured the incorporation of ^3H_2O into lipids in liver, blood and parametrial adipose tissue during the last 3 days of gestation. Since ^3H_2O freely crosses the placental barrier, the rates of lipogenesis *in vivo* in some foetal tissues have been estimated at the same time.

The aim of the present work was to study the possible relationship between maternal and foetal lipogenesis during the days before parturition. The rates of lipogenesis in foetal tissues have also been studied as indicators of the development of foetal tissues towards adaptation to extrauterine life.

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Experimental

Albino Wistar rats fed on a stock laboratory diet were killed for the experiments between 09:00 and 10:00 h. Conception was assumed by the presence of spermatozoa in the vagina, and gestational age was confirmed by the foetal weight. Virgin (200–250 g) and pregnant (300–350 g) rats were injected intraperitoneally with 5 mCi of ^3H_2O (The Radiochemical Centre, Amersham, Bucks., U.K.). After 50 min rats were anaesthetized with Nembutal (50 mg/kg body wt.), and 10 min later the abdomen was opened and maternal blood was collected from the aorta. Foetuses were delivered by rapid hysterectomy. Then samples of maternal and foetal tissues were taken. Samples of tissue (1 g) or of heparinized blood (1 ml) were added to 3 ml of 30% (w/v) KOH, and the lipid was saponified and extracted by the method of Stansbie *et al.* (1976).

Plasma insulin was measured by radioimmunoassay by the method of Hales & Randle (1963), with human insulin as the standard. Plasma progesterone was measured by radioimmunoassay with a kit purchased from Nordiclab (Oulu, Finland). Human progesterone was used as the standard (Hammond *et al.*, 1977). Non-esterified plasma fatty acids were assayed by the colorimetric method of Itaya & Ui (1965). Plasma triacylglycerols were extracted and saponified by the method of Eggstein & Kreutz (1966). Free glycerol was measured by enzymic assay (Garland & Randle, 1962). Neutralized $HClO_4$ extracts were used for the determination of glucose by the glucose oxidase method (Krebs *et al.*, 1963, 1964).

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Results and discussion

Rates of lipogenesis in maternal tissues

The rates of lipogenesis decreased in pregnant-rat liver during the transition from 20 to 22 days of gestation ($P < 0.001$), but the incorporation of ^3H_2O into lipid increased in parametrial adipose tissue during the same period ($P < 0.01$). After 22 days of gestation, the rate of lipogenesis in the liver was significantly lower than that in fed virgin rats ($P < 0.01$), and the incorporation of ^3H_2O into lipid in adipose tissue was restored to those values found in fed virgin rats (Table 1). The incorporation of ^3H_2O into blood lipid may be an indicator of the rate of export of lipid previously synthesized by the liver during the time of the experiment. If so, the decrease in hepatic lipogenesis observed during the last few days of gestation resulted in a decrease in the release of liver lipid into the blood (Table 1). The rate of lipogenesis in the liver increased 2-fold 1 day *post partum* as compared with values found after 22 days of gestation. The rate was also higher than those observed in virgin rats ($P < 0.05$; Table 1). No changes were observed 1 day *post partum* in the rate of lipogenesis in adipose tissue, as compared with those values found after 22 days of gestation (Table 1). The inhibition of hepatic lipogenesis during late gestation observed in our experiments is in agreement with the previous work of Fain & Scow (1966) in the period 16–20 days of gestation. However, the increased rate of incorporation of ^3H_2O into lipid observed in our experiments in adipose tissue during late gestation clearly contrasts with the inhibition of lipogenic capacity of adipose tissue between days 16 and 20 of gestation found by Fain & Scow (1966). The changes in the rates of lipogenesis of liver and adipose tissue occurring during late gestation may account for the changes in the concentrations of plasma lipid observed in these circumstances. Thus plasma triacylglycerols decreased between days 21 and 22 of gestation (Table 2), when hepatic lipogenesis decreased to values below those observed in virgin rats (Table 1). In addition, the increase in lipoprotein lipase activity observed in the mammary gland during this period (Hammosh *et al.*, 1970) may also contribute to the decrease in plasma triacylglycerol concentrations. Likewise, plasma non-esterified fatty acids decreased by 50% in the last day of gestation (Table 2), when the rate of lipogenesis in adipose tissue increased up to that in virgin rats (Table 1). The changes in the rate of hepatic lipogenesis observed during the last 2 days of gestation seem to be related to plasma insulin concentrations. Thus the decrease in liver lipogenesis (Table 2) parallelled the decrease of plasma insulin concentrations (Table 2). This decrease of insulin might itself explain the inhibition observed in liver lipogenesis, because insulin is clearly involved in the regulation of liver lipogenesis *in vivo* (Stansbie *et al.*, 1976). Whether other hormones as well as insulin are involved in the decrease of liver lipogenesis during late gestation remains to be established. However, the rate of lipogenesis in adipose tissue (Table 1) does not seem to correlate with plasma insulin concentrations (Table 2). This is not unexpected, because a marked resistance of rat adipose tissue to insulin during late gestation owing to the antagonism of some placental and maternal hormones has been reported (Costrini & Kalkhoff, 1971; Flint *et al.*, 1979). The concentrations of progesterone decreased significantly during the last day of gestation (Table 2; Sutter-Dub *et al.*, 1973; Martin *et al.*, 1977), a fact that may account for the increase in the rate of lipogenesis in adipose tissue observed during the same period. Thus the decrease in progesterone concentrations could weaken the resistance of adipose tissue to insulin and restore the rate of lipogenesis during the day before parturition. If so, the decrease of blood glucose concentration observed during this period may be due to the increase in glucose demand by maternal adipose tissue.

Table 1. *Rates of lipogenesis in vivo in maternal and foetal tissues during late gestation and after parturition in the rat*
For details see the Experimental section. The results are means ± S.E.M. ($n = 6$–10). Rates of lipogenesis are expressed as μmol of ^3H_2O incorporated into lipid/h per g wet wt. of tissue or per ml of whole blood. Values that are significantly different by Student's t test from those for virgin rats or from those for foetuses after 20 days of gestation are shown: $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

	Maternal tissues			Foetal tissues		
State of rats	Liver	Blood	Adipose	Placenta	Liver	Lung
Virgin	17.0 ± 1.6	1.1 ± 0.2	10.7 ± 1.2	—	—	—
Pregnant						
20 days	27.9 ± 1.2***	3.2 ± 0.4**	6.4 ± 0.3**	4.8 ± 0.4	18.4 ± 0.9	6.4 ± 0.3
21 days	18.6 ± 1.7	3.2 ± 0.3**	7.5 ± 0.6*	3.8 ± 0.3*	12.4 ± 1.2**	8.0 ± 0.6**
22 days	10.8 ± 0.7**	1.5 ± 0.1	10.7 ± 1.0	3.6 ± 0.1*	7.6 ± 0.9**	8.2 ± 0.7**
1 day *post partum*	22.5 ± 2.5*	3.3 ± 0.5**	12.6 ± 1.2	—	—	—

Table 2. *Concentrations of metabolites and hormones in plasma during late gestation and after parturition in the rat*
Blood was collected from the aorta, and the metabolites and hormones were determined as described in the Experimental section. The results are means ± S.E.M. ($n = 6$–10). Values that are significantly different by Student's t test from those for virgin rats are shown: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

State of rats	Glucose (μmol/ml)	Non-esterified fatty acids (μmol/ml)	Triacylglycerols (μmol/ml)	Insulin (μunits/ml)	Progesterone (ng/ml)
Virgin	7.4 ± 0.2	0.27 ± 0.05	1.5 ± 0.1	25.6 ± 3.6	25.4 ± 4.1
Pregnant					
20 days	6.3 ± 0.3*	1.08 ± 0.07***	5.3 ± 0.4***	93.3 ± 14.0***	56.4 ± 7.4**
21 days	6.4 ± 0.1*	1.83 ± 0.33***	6.0 ± 0.2***	65.8 ± 16.5*	167.2 ± 35.9***
22 days	5.0 ± 0.2***	0.96 ± 0.06***	1.7 ± 0.1	37.0 ± 6.7	25.9 ± 2.5
1 day *post partum*	6.9 ± 0.1	—	2.5 ± 0.3	26.6 ± 6.4	7.5 ± 1.0**

Rates of lipogenesis in foetal tissues

The hyperlipaemia found in the pregnant rat (Knoop *et al.*, 1973) contrasts with the low concentrations of plasma lipid in the foetal circulation. The transport of maternal lipid to the rat foetus is lower than in other mammals such as the rabbit or the guinea pig (Koren & Shafrir, 1964; Jones, 1976). Therefore the incorporation of maternal lipid into foetal tissues is likely to be secondary to lipogenesis *de novo* from maternal carbohydrates. In addition, the incorporation of $^{3}H_2O$ into placental lipid was significantly lower than in the liver or lung of the foetus (Table 1), which suggests that placental lipogenesis was insignificant during late gestation. Consequently, these results seem to support the idea that lipids of foetal tissues are synthesized *in situ* from maternal carbohydrates in the rat.

The rate of lipogenesis *de novo* in foetal liver after 20 days of gestation was similar to those found in virgin rats (Table 1). However, the rate of lipogenesis decreased significantly during the last 2 days of gestation, to values half those observed after 20 days of gestation. This decrease was parallel to those observed in the rate of lipogenesis in maternal liver in the same circumstances, suggesting that the decrease observed in foetal-liver lipogenesis is not likely to be due to competition by maternal-liver lipogenesis for the substrate. Conversely, the increase in the rate of lipogenesis observed in maternal adipose tissue (Table 1) may contribute to the decreased substrate availability for foetal-liver lipogenesis. Actually, the decrease in maternal blood glucose is concurrent with the increase of the rate of lipogenesis in adipose tissue, which occurred in the last day of gestation. It should be mentioned that the volume of adipose tissue is greatly increased in the pregnant rat (Beaton *et al.*, 1954), which may result in the enhancement of the substrate demand of the tissue. On the other hand, foetal liver accumulates glycogen during the last 3 days of gestation (Devos & Hers, 1974), which may also contribute to the decrease in glucose availability for foetal-liver lipogenesis.

Foetal-lung lipogenesis increased during days 20–21 of gestation, which may be related to maturation of lung structures before parturition (Maniscalco *et al.*, 1978; Weinhold *et al.*, 1980).

In conclusion, our results suggest that the rate of maternal-liver lipogenesis remains high, whereas adipose-tissue lipogenesis is depressed, presumably as a consequence of the enhancement of lipolysis in this tissue. Later, when the rate of lipogenesis in adipose tissue increases, the rate of hepatic lipogenesis fell, to values below those observed in virgin rats. The rate of liver lipogenesis increased again immediately after parturition, presumably to support the synthesis of milk lipid before mammary-gland lipogenesis was enhanced. On the other hand, the changes observed in the rates of lipogenesis in foetal tissues before parturition are consistent with the adaptation to the neonatal situation, when lipids are supplied by maternal milk and the efficiency of lung ventilation depends on the maturity of the lung alveoli.

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