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Oleate metabolism in hepatocytes isolated from newborn rabbits submitted to various physiological conditions

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Previous studies using isolated rabbit hepatocytes have shown that the rate of ketone body synthesis is very low at birth and increases markedly to maximal levels 12-24 h after birth. This developmental pattern is triggered by birth-associated factors rather than by a given stage of foetal maturation (El Manoubi, Ferré and Girard, 1981 ; Duée *et al.*, (1985). However, ketone bodies are only one of the final products of fatty acid metabolism in the hepatic cells. Moreover, it has been reported that in adult rat liver the metabolic fate of fatty acids is regulated by the plasma glucagon/insulin ratio (McGarry and Foster, 1980). The aim of the present work was to answer the following questions : (1) what is the metabolic fate of oleate in hepatocytes isolated from newborn rabbits and (2) are pancreatic hormones involved in the emergence of ketogenesis after birth.

Rabbits of the New Zealand White strain were delivered by caesarean section either at term (32 days postcoitum) or postmaturely (34 days postcoitum). Postmaturity was induced by injecting pregnant does with progesterone (1.25 mg/kg/day) during the last 4 days of gestation and for 2 days after normal term. Hepatocytes, isolated as described by El Manoubi *et al.* (1983) at delivery (term and postmature newborns) or 24 h after birth (starved newborns) were incubated at 37 °C for 60 min in the presence of [1-^{14}C] oleate (1 mM), in a final volume of 4 ml of Krebs-Henseleit buffer.

In each of the physiological conditions studied, i.e. term newborn, postmature newborn, or 24-hour old fasting newborn, the total amount of [1-^{14}C] oleate metabolized was similar. The rate of oleate oxidation was low (7 %) in hepatocytes isolated from term newborns at birth and was increased 7-fold, that is to 55 %, in 24-hour old fasting newborns. Conversely, the incorporation of [1-^{14}C] oleate into triacylglycerols and phospholipids, high at birth (93 % of oleate metabolized), was decreased by approximately 50 % during the first day of extrauterine life (45 % of oleate metabolized in hepatocytes isolated from 24-hour old term newborns).

In order to answer the second question, we studied the metabolism of [1-^{14}C] oleate in hepatocytes isolated from postmature newborns. It has been shown in rats that postmaturity induces the hormonal changes *in utero* that occur spontaneously in newborns, *i.e.* increased glucagon and decreased insulin levels (Portha, Picon and Rosselin, 1978).

The rate of ketone body production from 1 mM oleate was 4-fold higher in hepatocytes isolated from postmature newborns at birth (111 $\pm$ 20 nmol/h/10^6 hepato.) than in those isolated from term newborns (25 $\pm$ 9 nmol/h/10^6

hepato.). This resulted from an increased rate of oleate oxidation (27 % of oleate metabolized) which became intermediate between term newborns at birth and 24-hour old fasting newborns.

In conclusion, the increase in the rate of ketone body production in newborn rabbit hepatocytes did not result from increased oleate metabolism but from a change in the distribution of oleate between esterification and oxidation. The redirection of oleate towards oxidation could be regulated by relative changes in the level of pancreatic hormones which occur after birth or after prolonged pregnancy.

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