Octanoate and palmitate as substrates for ketogenesis by hepatocytes isolated from suckling rabbits

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The lactating rabbit synthesizes milk triacylglycerol, which contains a high proportion (approx. 65 mol/100 mol) of medium-chain fatty acids, the remainder being long-chain fatty acids (Smith et al., 1968). Experiments in vivo with suckling rabbits had shown that medium-chain milk fatty acids were transported to the liver via the hepatic portal vein, and were taken up by the liver. In order to compare the metabolism of medium- and long-chain fatty acids by the liver, octanoate (C₁₈:0) and palmitate (C₁₆:0) were incubated at a concentration of 1 mM with hepatocytes obtained from 10–12-day-old rabbits and rates of oxidation to CO₂ and of ketone-body production were measured. This is a period of development when ketone bodies were not affected substantially. There was a tendency for the proportion of radioactivity in 14C0₂ from [1-14C]octanoate to increase in the presence of palmitate compared with incubations with [1-14C]octanoate alone. The results suggest that a proportion of the octanoate and palmitate utilized had not been accounted for as CO₂, ketone bodies or lipids. This was investigated by passing the acid-soluble material from the hepatocytes plus incubation medium through a mixed resin of anion- and cation-exchange material which would remove any charged metabolites. After incubation for 60 min with [1-14C]octanoate, about 20% of the initial radioactivity was not retained by the resin, and it would be interesting to know if this eluate contained, for example, glucose. The inclusion of 1 mM unlabelled palmitate in addition to the 1 mM-1-14Cloctanoate in the incubation medium decreased the radioactivity eluted from the resin to 20% to 2%. Very little radioactivity was eluted from the resin when hepatocytes were incubated with [1-14C]palmitate.

The results as a whole suggest that octanoate and palmitate are metabolized differently by the hepatocytes. The finding that less palmitate carbon was recovered as CO₂ and ketone bodies from the 1-14C-labelled fatty acids that was recovered as 14CO₂ was much lower than the amount recovered in ketone bodies. Octanoate produced almost four times as much 14CO₂ as did palmitate. Neither fatty acid appeared to be esterified into phospholipid or converted into cholesterol. Octanoate was neither elongated nor esterified into triacylglycerol, and palmitate was only esterified into triacylglycerol at very low rates.

To investigate whether the presence of fatty acids of both of these chain lengths influences the metabolism of either of them, hepatocytes were incubated in the presence of either 1 mM-1-[1-14C]octanoate plus 1 mM-palmitate or 1 mM-1-[1-14C]-palmitate plus 1 mM-octanoate. When hepatocytes were incubated in the presence of both fatty acids the amount of each fatty acid metabolized was depressed by up to 50%. However, the proportion of radioactivity recovered in the ketone bodies was not affected substantially. There was a tendency for the proportion of radioactivity in 14CO₂ from [1-14C]octanoate to increase in the presence of palmitate compared with incubations with [1-14C]octanoate alone. The results suggest that a proportion of the octanoate and palmitate utilized had not been accounted for as CO₂, ketone bodies or lipids. This was investigated by passing the acid-soluble material from the hepatocytes plus incubation medium through a mixed resin of anion- and cation-exchange material which would remove any charged metabolites. After incubation for 60 min with [1-14C]octanoate, about 20% of the initial radioactivity was not retained by the resin, and it would be interesting to know if this eluate contained, for example, glucose. The inclusion of 1 mM unlabelled palmitate in addition to the 1 mM-[1-14C]octanoate in the incubation medium decreased the radioactivity eluted from the resin to 20% to 2%. Very little radioactivity was eluted from the resin when hepatocytes were incubated with [1-14C]palmitate.

The results as a whole suggest that octanoate and palmitate are metabolized differently by the hepatocytes. The finding that less palmitate carbon was recovered as CO₂ and ketone bodies than was the case with octanoate could reflect the different modes of entry of the two fatty acids into mitochondria. Long-chain fatty acids are transported by the carnitine acyltransferase system, whereas medium-chain fatty acids appear to cross freely the mitochondrial inner membrane (Pande & Parvin, 1980).

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Fig. 1. Total ketone-body production (lactoacetate plus D-(-)-3-hydroxybutyrate) from octanoate or palmitate

Hepatocytes (3 x 10⁶ cells) from 10–12 day-old rabbits were incubated with 1 mM-octanoate (O) or with 1 mM-palmitate (●) in 3 ml of Medium 199 at 37°C.

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