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Lipid Metabolism in Experimental Cholestasis

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Disturbances in lipid metabolism have been reported in human and experimental obstructive jaundice. Thus human studies have shown elevated concentrations of plasma free fatty acids (Mortiaux & Dawson, 1961), serum triglycerides (Mendenhall & Mortiaux, 1961) and cholesterol (Man, Kartin, Durlacher & Peters, 1945), whereas in animal experiments elevated concentrations of cholesterol (Byers, Friedman & Michaelis, 1951) and abolition of the negative-feedback regulation of cholesterol biosynthesis (Katterman & Creutzfeldt, 1970) have been described. The purpose of the present investigation was to study lipid and ketone-body metabolism in the rat during experimental cholestasis.

Bile-duct ligation or sham operations were performed on anaesthetized rats and the animals were killed 6–9 days later. All rats were starved for 48h before being killed. Blood was collected from one group for determinations of triglycerides, free fatty acids, cholesterol and bilirubin and enzymic analysis of blood metabolites. The mean bilirubin concentration in the ligated animals was 9mg/100ml.

Another group of animals were killed by cervical dislocation, and the livers were freeze-clamped between clamps cooled in liquid N₂ and metabolites were determined in the deproteinized liver extracts by enzymic methods.

The most striking change noted was a fall in blood and liver ketone-body concentrations to 31 and 28% respectively compared with the corresponding values for the sham-operated rats after 9 days of biliary stasis. This was accompanied by a 73% decrease in hepatic acetyl-CoA concentration. The [3-hydroxybutyrate]/[acetoacetate] ratio fell from 2.7 to 1.1 and this was associated with a fall in the [glutamate]/[2-oxoglutarate][NH₄⁺] ratio consistent with a more oxidized mitochondrial [free NAD⁺]/[free NADH] ratio (Williamson, Lund & Krebs, 1967). The [lactate]/[pyruvate] ratios remained unchanged. Concentrations of plasma free fatty acids were normal or only slightly lower than in the controls, whereas those of plasma triglycerides and serum cholesterol were increased (146 and 200% respectively).

These results suggest a decrease in the β -oxidation of fatty acids and a stimulation of cholesterol and triglyceride synthesis. Possible mechanisms for these metabolic alterations will be discussed.

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An Explanation for the Lowering of Blood Ketone-Body Concentrations in Starved Rats during Short-Term Exercise

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The fall in blood ketone-body concentrations (45%) in starved rats during short-term exercise was ascribed by Drury, Wick & MacKay (1941) to increased peripheral utilization of ketone bodies. However, electrical stimulation of isolated perfused rat skeletal muscle does not increase ketone-body uptake (Houghton & Ruderman, 1970). Short-term severe exercise is also characterized by a rise in circulating lactate concentration (up to about 10mM), and as lactate can have an anti-lipolytic action (Bjorntrop, 1966) the effect of infusion of L(+)-lactic acid into resting starved (48h) rats was investigated. A concentration of about 7mM was reached in 10min and maintained for a further 20min. Blood ketone-body concentrations fell from 4.51 ± 1.51 mM (mean $\pm$ S.D., five observations) to 2.29 ± 0.55 mM by 10min and to 1.03 ± 0.41 mM at 30min. There was a concomitant decrease in the plasma free fatty acid concentration from 1.40 ± 0.23 μ equiv./ml to 0.74 ± 0.18 μ equiv./ml after 30min infusion. On cessation of infusion there was a rise in the free fatty acid and ketone-body concentrations.

The results suggest that the fall in the concentration of blood ketone bodies during short-term exercise is mainly due to an inhibition of free fatty acid release from adipose tissue and perhaps also to a direct anti-ketogenic effect of lactate on the liver.

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