Regulation of hepatic lipogenesis in starved and diabetic animals by thyroid hormone

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The effects of intragastric feeding with glucose and of the administration of L-triiodothyronine (T_3) on in vivo rates of hepatic lipogenesis were investigated in control (fed ad libitum on normal diet), diabetic (fed ad libitum on normal diet), fat-fed (fed ad libitum on high-fat diet), and starved (food removed for 48 h) rats. Two days of T_3 treatment increased hepatic lipogenesis in control and fat-fed animals but not in the diabetic or starved animals, although increases in lipogenesis in diabetic animals were observed after 4 days of T_3 treatment.

Intragastric glucose feeding increased hepatic lipogenesis in the livers of control animals and T_3-treated control animals. Such increases are mediated by an increase in the circulating insulin concentration, as increases are not observed in diabetic rats or T_3-treated diabetic rats. Glucose feeding failed to increase hepatic lipogenesis in fat-fed rats or starved rats. Insulin injection together with glucose feeding increased lipogenesis in the fat-fed group but not the starved group; i.e., impaired insulin secretion following an oral glucose load may in part explain the lack of response in the fat-fed but not the starved animals. Marked increases in hepatic lipogenesis after glucose feeding were, however, observed if either the starved or the fat-fed animals were treated with T_3. The physiological implications of these observations are discussed.

Rates of hepatic lipogenesis depend on a variety of nutritional and hormonal factors (for reviews see Bloch & Vance, 1977; Geelen et al., 1980). Rates of hepatic fatty acid synthesis are decreased in starved (Allmann et al., 1965), diabetic (Nakanishi & Numa, 1970), and hypothyroid (Volpe & Marasa, 1975) animals and in animals fed a high-fat diet (Carrozza et al., 1979). Conversely, rates of hepatic
lipogenesis are increased by administration of thyroid hormones (Roncari & Murthy, 1975) or feeding a diet high in carbohydrate (see Oppenheimer et al., 1981). The decreased lipogenic rates observed in diabetes and on starvation are partly caused by decreased concentrations of acetyl-CoA carboxylase (EC 6.4.1.2) and fatty acid synthetase. It has been found that administration of L-triiodothyronine (T₃) to diabetic rats restores the concentration of these enzymes to the levels found in non-diabetic animals (Das, 1980). We therefore studied the effects of such treatment on the rates of hepatic lipogenesis observed in vivo. For comparison, the effects of T₃ treatment on the rates of hepatic lipogenesis of starved and fat-fed animals were investigated.

Experimental

Female albino Wistar rats (150-200 g), subjected to a 12-h-light:12-h-dark cycle (light period starting at 0800 h), were fed ad libitum on standard rodent diet (Rat/Mouse No. 3) or a high-fat diet (30% butter and 70% Rat/Mouse No. 3) purchased from BP Nutrition (U.K.) Ltd., Strepfield, Witham, Essex, U.K. Although the crude-protein content of the high-fat diet was 30% less than that of the control diet, the growth rate was unaffected, and weight increases of 5.9 ± 0.2% (3 animals) and 5.6 ± 0.6% (3 animals) of the initial body weights were observed in, respectively, control and fat-fed animals over 7 days. In some experiments, food was withdrawn for 48 h; the rats were transferred to clean cages at the onset of food withdrawal to minimize coprophagia, and the dietary status of the starved animals was assessed by measurements of blood ketone body levels (see text) and hepatic glycogen content [6.2 ± 2.8 (5 animals) μmol glucose/g wet wt.]. Diabetes was induced by the intravenous administration of streptozotocin (60 mg/kg body wt.; in 0.1 M sodium citrate buffer, pH 4.5) and confirmed by whole-blood glucose concentrations greater than 15 mM, and experiments were initiated on the third day after streptozotocin injection. Animals were made hyperthyroid by subcutaneous injection of T₃ [100 μg/100 g body wt./day; in 10 mM NaOH/0.03% bovine serum albumin (BSA)]. This dose of T₃ produced moderate (6-10%) hyperphagia in all groups and slight (1-3%) weight loss in the starved and diabetic groups. Treatment was for 2 or 4 days (animals killed on day 3 or 5). Some animals were treated with T₃ for 10 days. Such treatment was not routinely carried out as the rates of hepatic lipogenesis were not significantly different from those observed in rats treated for 4 days (results not shown). T₃ treatment of the starved rats was initiated at the time of food withdrawal. Control ( euthyroid) rats were injected with an equivalent volume of 10 mM NaOH/0.03% BSA. All experiments were started between 0900 h and 0930 h. Glucose (2 mmol/100 g body wt.; 2 M solution) or H₂O (1 ml/100 g body wt.) were administered intragastrically as described by Sugden et al. (1981). Insulin (2 units; Isophane insulin injection, Nordisk Insulin Laboratorium, Copenhagen, Denmark) was injected subcutaneously at this time except for the starved rats, where insulin was injected 15 min after glucose loading to avoid lethal