The relationship between fat synthesis and oxidation in the liver after re-feeding and its regulation by thyroid hormone

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The administration of glucose to 48 h-starved euthyroid or hyperthyroid rats led to decreased blood concentrations of fatty acids and ketone bodies in both groups, but fatty acid concentrations were higher and ketone-body concentrations lower in the latter group. Decreased ketonaemia was not due to increased ketone-body clearance. Flux through carnitine palmitoyltransferase 1 was increased, consistent with the effects of hyperthyroidism on enzyme activity demonstrated *in vitro*. Correlations between the concentrations of ketone bodies and long-chain acylcarnitine measured in freeze-clamped liver samples indicated that a lower proportion of the product of β -oxidation was used for ketone-body synthesis. Citrate concentrations were unaffected by hyperthyroidism, but lipogenesis was increased. The results are discussed in relation to the factors controlling hepatic carbon flux and energy requirements after re-feeding.

INTRODUCTION

The ability of the liver to metabolize carbohydrate may be restricted during the transition from the starved to the fed state. It is well established that, on re-feeding after starvation, high rates of gluconeogenesis persist [1,2], the concentration of fructose 2,6-bisphosphate remains depressed [3], and the pyruvate dehydrogenase complex (PDH) is not immediately re-activated [4,5]. While the use of carbohydrate as energy substrate is precluded, and lipogenesis remains low (see [1]), the capacity for mitochondrial fat oxidation continues to be high. Low concentrations of malonyl-CoA, a lipogenic intermediate, maximize flux through the overt form of carnitine palmitoyltransferase (CPT 1) [6,7]. Furthermore, both the maximal activity and the regulatory characteristics of CPT 1 continue to resemble those found in the starved state for at least 6 h after re-feeding [8]. In contrast, the intrinsic capacity of the liver to oxidize fatty acids rapidly declines [9]. Therefore, an intramitochondrial site of control of ketogenesis may assume greater regulatory importance.

The response of the liver of hyperthyroid rats to re-feeding differs from that normally observed in euthyroid rats in several important respects. Notably, glucose re-feeding of starved hyperthyroid rats stimulates hepatic lipogenesis [10,11], and, although PDH remains inactive, evidence has been provided for increased PDH phosphatase activity [5]. Paradoxically, in the fed state at least, hyperthyroidism also increases the activity of CPT 1, although the importance of this effect of the hormone on flux through the enzyme *in vivo* has not been assessed. Well-documented effects of hyperthyroidism on CPT 1 include increased maximal activity and decreased sensitivity to inhibition by malonyl-CoA [12,13], effects which are qualitatively similar to those observed in response to starvation in euthyroid rats.

In the present study we have measured rates of lipogenesis, in conjunction with the concentrations of

long-chain acylcarnitine, citrate and ketone bodies, in order to examine the relationship between lipogenesis, mitochondrial fat oxidation and ketogenesis after the intragastric administration of glucose to 48 h-starved rats. In the same experiments we monitored the activity of PDH in order to assess the contribution of acetyl-CoA derived from carbohydrate as ketogenic and/or lipogenic substrate. A comparison was made between the responses of livers from normal (euthyroid) rats, and rats made hyperthyroid by the administration of tri-iodothyronine (T_3).

MATERIALS AND METHODS

Materials

Sources of materials were as in [11]. The NEFA assay kit was from Alpha Laboratories, Eastleigh, Hants, U.K. 3-Mercaptopicolinic acid (MPA) was generously provided by Dr. M. Bird, Glaxo Group Research, Greenford, Middx., U.K.

Treatment of rats

Female albino Wistar rats (180–220 g) were starved for 48 h (in grid-bottomed cages). Rats were made hyperthyroid by the subcutaneous injection of T_3 (100 μ g/100 g body wt. per day, dissolved in 10 mM-NaOH/0.03 % bovine serum albumin) during the period of starvation as described previously [11]. Controls were injected with the solvent.

Experiments were started on day 3 between 08:30 and 09:30 h, when glucose (2 mmol/100 g body wt.; 2 M soln.) or water (1 ml/100 g body wt.) was administered intragastrically under light diethyl ether anaesthesia (see [5,11]). Rats were killed at 0.5 h intervals for up to 2.5 h after the intragastric load, after anaesthesia for 5 min with sodium pentobarbital (6 mg/100 g body wt.). MPA was administered as the sodium salt by intraperitoneal

Abbreviations used: PDH, pyruvate dehydrogenase complex; NEFA, non-esterified fatty acids; MPA, 3-mercaptopicolinic acid; T_3 , tri-iodothyronine; CPT 1, carnitine palmitoyltransferase 1.

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injection in conjunction with the glucose load as described previously [1].

Functional hepatectomies

Rats were anaesthetized with sodium pentobarbital (6 mg/100 g body wt.), and blood (0.25 ml) was sampled from the anterior vena cava. They were then subjected to functional hepatectomy as described in [14]. The decline of blood ketone-body concentrations was monitored from 4 to 30 min after functional hepatectomy, with sampling from the vena cava (see [15] for details). In sham-operated controls ligatures were placed around the appropriate vessels but not tied. Rates of ketone-body removal were calculated over the first 7.5 min after functional hepatectomy as in [15]. Ketone-body concentrations were unchanged at 7.5 min in the sham-operated controls.

Lipogenesis

Rates of lipogenesis were estimated as ^3H incorporation from $^3\text{H}_2\text{O}$ into tissue saponifiable fatty acid as described in [16]. Rats were anaesthetized with pentobarbital, arterial blood samples were withdrawn for the determination of the specific radioactivities of plasma $^3\text{H}_2\text{O}$, and liver was sampled at 2 h after the intragastric glucose load.

Enzyme assays

PDH complex (active form, PDH_a) and citrate synthase activities were measured in freeze-clamped liver extracts as described in [17]. PDH_a activities are expressed relative to citrate synthase to correct for possible differences in mitochondrial content/extraction (see, e.g., [4,5,17]). Total PDH activity is unaffected by hyperthyroidism [5,18]. A unit of enzyme activity is that which converts 1 μmol of substrate into product/min at 30 °C.

Metabolite assays

Plasma obtained at the time of sampling was assayed for NEFA. Concentrations of the ketone bodies (D-3-hydroxybutyrate and acetoacetate) were determined in KOH-neutralized HClO_4 extracts of whole blood. Concentrations of the ketone bodies, citrate and long-chain acylcarnitine were measured in extracts of freeze-clamped liver (see [15,19] for details of methods). Rats were sampled at 0.5 h intervals for up to 2.5 h after the intragastric load.

Statistical analysis

Statistical significance of differences was assessed by Student's unpaired t test. Results are means $\pm$ S.E.M. for the numbers of rats (n) indicated.

RESULTS AND DISCUSSION

Lipid fuel availability and utilization after re-feeding in hyperthyroidism

The administration of glucose to starved euthyroid rats elicited the expected decline in blood NEFA and ketone-body concentrations (Table 1). Experimental hyperthyroidism was associated with higher concentrations of NEFA both in the fed state and in starved rats after glucose administration (Table 1). Whereas in rats fed *ad libitum* ketonaemia was also increased, blood and hepatic ketone-body concentrations after re-feeding were significantly lower in the T_3 -treated rats (Tables 1 and 2). Hepatic blood flow is not decreased in hyperthyroidism [20]. Moreover, in a parallel series of experiments, it was observed that increases in NEFA concentrations after functional hepatectomy of glucose re-fed hyperthyroid rats were similar to those observed in glucose-re-fed euthyroid rats (results not shown). Thus decreased ketonaemia in hyperthyroid rats after re-feeding is not secondary to decreased precursor supply or hepatic fatty acid uptake. Further experiments indicated that rates of disappearance of ketone bodies from the blood of functionally hepatectomized rats were unaffected by the thyroid status (Fig. 1a). The clearance of acetoacetate (the preferred substrate) was proportional to its initial concentration, with no indication of increased utilization in hyperthyroidism (Fig. 1b). The altered relationship between NEFA and ketone-body concentrations after re-feeding therefore suggests that, for any given rate of hepatic fatty acid utilization, a smaller proportion of fatty acyl-CoA is used for ketogenesis.

Acylcarnitine concentrations

Inhibition of CPT 1 by malonyl-CoA plays a key role in the restriction of mitochondrial fatty acid oxidation in livers of fed rats. This type of control may be less important in starvation, where malonyl-CoA sensitivity is decreased [21–24] and CPT I maximal activity is increased [21,25]. Although in some circumstances malonyl-CoA concentrations and lipogenic rates are not

Table 1. Effects of T_3 treatment on blood NEFA and ketone-body concentrations in glucose-re-fed 48 h-starved rats

For experimental details see the text. Results are means $\pm$ S.E.M. for six to nine rats. Statistically significant effects of T_3 treatment are indicated by $\dagger P < 0.05$; $\dagger\dagger P < 0.01$, and effects of glucose administration are indicated by $^{**} P < 0.01$; $^{***} P < 0.001$.

Nutritional status	Treatment	Time of sampling (h)	Blood metabolite concn. (mM)			
			NEFA		Ketone bodies	
			Control	T_3 -treated	Control	T_3 -treated
Fed 48 h-starved	Water	1.0	0.19 $\pm$ 0.03	0.49 $\pm$ 0.08 $\dagger\dagger$	0.25 $\pm$ 0.04	0.44 $\pm$ 0.09
	Water	1.0	0.58 $\pm$ 0.05	0.51 $\pm$ 0.04	2.56 $\pm$ 0.33	2.09 $\pm$ 0.15
	Glucose	0.5	0.23 $\pm$ 0.04 ***	0.31 $\pm$ 0.04 **	0.83 $\pm$ 0.21 ***	0.43 $\pm$ 0.10 $^{***}\dagger\dagger$
	Glucose	1.0	0.18 $\pm$ 0.02 ***	0.23 $\pm$ 0.03 $^{***}\dagger$	0.54 $\pm$ 0.13 ***	0.16 $\pm$ 0.05 $^{***}\dagger\dagger$
	Glucose	1.5	0.14 $\pm$ 0.05 ***	0.27 $\pm$ 0.04 ***	0.24 $\pm$ 0.03 ***	0.21 $\pm$ 0.03 ***
	Glucose	2.0	0.19 $\pm$ 0.06 ***	0.30 $\pm$ 0.03 **	0.42 $\pm$ 0.12 ***	0.31 $\pm$ 0.06 ***

Table 2. Effects of T_3 treatment on hepatic long-chain acylcarnitine and ketone-body concentrations, and 3-hydroxybutyrate/acetoacetate concentration ratios, in glucose-re-fed 48 h-starved rats

For experimental details see the text. Results are means $\pm$ S.E.M. for seven to nine rats. Statistically significant effects of T_3 treatment are indicated by $\dagger P < 0.05$, $\dagger\dagger P < 0.01$, $\dagger\dagger\dagger P < 0.001$, and effects of glucose administration are indicated by $*P < 0.05$, $**P < 0.01$; $***P < 0.001$.

Nutritional status	Treatment	Time of sampling (h)	Long-chain acylcarnitine concn. (nmol/g wet wt.)		Ketone-body concn. (μ mol/g wet wt.)		[3-Hydroxybutyrate]/[acetoacetate]	
			Control	T_3 -treated	Control	T_3 -treated	Control	T_3 -treated
Fed	Water	1.0	19 $\pm$ 2	102 $\pm$ 9 $\dagger\dagger\dagger$	0.31 $\pm$ 0.07	0.46 $\pm$ 0.03	0.35 $\pm$ 0.04	0.44 $\pm$ 0.05
48 h-starved	Water	1.0	49 $\pm$ 4	83 $\pm$ 9 $\dagger\dagger$	1.74 $\pm$ 0.19	1.92 $\pm$ 0.10	1.79 $\pm$ 0.21	1.62 $\pm$ 0.10
	Glucose	0.5	32 $\pm$ 3*	50 $\pm$ 5 $\dagger\dagger\dagger$	1.25 $\pm$ 0.12*	0.88 $\pm$ 0.09 $\dagger\dagger\dagger$	0.91 $\pm$ 0.18**	0.42 $\pm$ 0.07 $\dagger\dagger\dagger$
	Glucose	1.0	18 $\pm$ 2**	61 $\pm$ 5 $\dagger\dagger\dagger$	1.03 $\pm$ 0.08**	0.67 $\pm$ 0.06 $\dagger\dagger\dagger$	0.28 $\pm$ 0.04***	0.35 $\pm$ 0.04***
	Glucose	1.5	23 $\pm$ 1***	58 $\pm$ 4 $\dagger\dagger\dagger$	0.94 $\pm$ 0.07**	0.65 $\pm$ 0.08 $\dagger\dagger\dagger$	0.22 $\pm$ 0.04***	0.29 $\pm$ 0.04***
	Glucose	2.0	31 $\pm$ 3*	65 $\pm$ 10 $\dagger\dagger$	1.02 $\pm$ 0.09**	0.90 $\pm$ 0.08***	0.35 $\pm$ 0.09***	0.48 $\pm$ 0.07***

Fig. 1. Changes in blood ketone-body concentrations after functional hepatectomy of euthyroid or hyperthyroid starved rats

(a) Rate of decline of blood acetoacetate (●, ○) or 3-hydroxybutyrate (▲, △) concentrations after functional hepatectomy of 48 h-starved rats. Mean rates of ketone-body clearance measured over the first 7.5 min after functional hepatectomy (see [15]) were 107 ± 11 nmol/min and 91 ± 15 nmol/min in control (●, ▲) and hyperthyroid (○, △) rats respectively ($P > 0.05$). (b) Relationship between initial acetoacetate concentrations and clearance rates. Rats were given water or medium-chain triacylglycerol by intragastric intubation under ether anaesthesia in order to achieve different concentrations of ketone bodies as in [15]. Clearance rates were measured over the first 7.5 min. ●, Euthyroid rats; ○, hyperthyroid rats. Regression analysis indicated a linear relationship between concentrations and clearance rates. The regression equations were: euthyroid rats, $y = 5.00 + 85.19x$, $r = 0.94$; hyperthyroid rats, $y = 11.90 + 93.15x$, $r = 0.93$. 3-Hydroxybutyrate clearance was also proportional to initial concentration, with no effect of hyperthyroidism (results not shown).

linked (see, e.g., [26]), others have noted that malonyl-CoA concentrations remain low after re-feeding [6,7], and, consistent with these latter findings, decreases in acylcarnitine in re-fed euthyroid rats (Table 2) were observed in the absence of increases in lipogenesis (Table 3). Decreased acylcarnitine formation is therefore more likely to reflect a decreased NEFA supply than a restraint on CPT 1 activity imposed by malonyl-CoA.

In hepatocytes, mitochondrial β -oxidation is proportional to long-chain acylcarnitine concentrations [27]. However, whereas starvation of euthyroid rats is associated with a 157% increase in long-chain acylcarnitine, hepatic ketone-body concentrations are increased by 461% (Table 2). Consequently, the ratio of ketone-body to acylcarnitine concentration ([KB]/[AC]) increases from 16.3 to 35.5. This implies that a greater proportion

Table 3. Effects of T_3 and MPA treatment on hepatic PDH_a activities, citrate concentrations and rates of lipogenesis in 48 h-starved rats

For experimental details see the text. Results are means $\pm$ S.E.M. for seven to nine rats. Statistically significant effects of T_3 treatment are indicated by $\dagger P < 0.05$, $\dagger\dagger P < 0.01$, and of MPA administration by $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. PDH_a values in fed control and fed hyperthyroid rats were 76.4 ± 8.4 and 83.2 ± 7.4 munits/unit of citrate synthase respectively. Hyperthyroidism and glucose re-feeding did not affect total PDH_a activities (results not shown).

Treatment	Time of sampling (h)	PDH _a (% of fed value)		Citrate concn. (μ mol/g wet wt.)		Lipogenesis (μ g-atoms of 3H /h per g wet wt.)	
		Control	T_3 -treated	Control	T_3 -treated	Control	T_3 -treated
Water	1.0	12.1 ± 0.8	11.4 ± 1.3	0.24 ± 0.02	0.20 ± 0.02	7.4 ± 0.6	$10.4 \pm 0.02\dagger\dagger\dagger$
Glucose	1.0	12.3 ± 1.0	14.5 ± 3.3	0.31 ± 0.02	0.35 ± 0.02	8.3 ± 0.9	$17.1 \pm 1.0\dagger\dagger\dagger$
Water	2.0	12.3 ± 2.2	15.0 ± 2.2	0.23 ± 0.03	0.24 ± 0.01	6.1 ± 0.7	$10.4 \pm 0.5\dagger\dagger\dagger$
Glucose	2.0	11.9 ± 2.2	8.5 ± 2.9	0.29 ± 0.02	0.33 ± 0.03	7.7 ± 0.5	$15.0 \pm 1.0\dagger\dagger\dagger$
Water + MPA	2.0	15.2 ± 5.4	14.3 ± 2.0	$0.40 \pm 0.02^{***}$	$0.89 \pm 0.05^{***\dagger\dagger\dagger}$	—	—
Glucose + MPA	2.0	14.5 ± 4.1	15.5 ± 1.6	$0.51 \pm 0.11^*$	0.40 ± 0.11	$26.5 \pm 2.5^{***}$	$40.8 \pm 1.7^{***\dagger\dagger\dagger}$

of the acetyl-CoA derived from acylcarnitine is being used for ketogenesis. The mean [KB]/[AC] ratio after glucose re-feeding was 42.3 ± 5.3 , suggesting that the liver continues in its ketogenic mode. A continued low activity of PDH_a (Table 3) precludes a major contribution of acetyl-CoA derived from carbohydrate as ketogenic substrate. The results therefore suggest that ketogenesis continues to be supplied by acetyl-CoA derived from fatty acids.

Long-chain acylcarnitine concentrations were not increased by starvation in hyperthyroid rats. In contrast, when T_3 was administered during the starvation period, substantial additional increases in concentrations were observed. Further experiments will reveal whether the additional effect of hyperthyroidism is achieved via synthesis of new enzyme protein, or through changes in the regulatory characteristics of the enzyme.

Although long-chain acylcarnitine concentrations were not increased by starvation in hyperthyroid rats, the [KB]/[AC] ratio was increased from 4.5 to 23.1, suggestive of increased intrinsic ketogenic capacity. The mean [KB]/[AC] ratio after re-feeding (13.4 ± 1.6) again exceeded the fed (hyperthyroid) value, but was considerably lower than that found in re-fed euthyroid controls. This implies that, after re-feeding, proportionally less of the acetyl-CoA derived from β -oxidation is used for ketogenesis in hyperthyroid compared with euthyroid rats. Concentrations of long-chain acylcarnitine at 1 h and 2 h after glucose administration were almost double those of the controls (Table 2), eliminating the possibility that decreased ketonaemia is a consequence of diminished acylcarnitine synthesis, and by implication acetyl-CoA production from fatty acids.

Regulation of CPT 1 *in vivo* in the liver of hyperthyroid rats

The increased maximal activity of CPT 1 occurring in response to hyperthyroidism should result in increased acylcarnitine synthesis even in the absence of changes in substrate concentration. Consistent with this, a higher concentration of long-chain acylcarnitine was observed for an equivalent NEFA concentration in hyperthyroid rats (Fig. 2; see also Table 2). Furthermore, as expected from the decreased sensitivity of CPT 1 to malonyl-CoA

Fig. 2. Relationships between plasma NEFA concentrations and hepatic acylcarnitine concentrations in euthyroid or hyperthyroid starved rats

For experimental details see the text. Rats were given glucose or water by intragastric intubation, and then sampled at intervals to obtain a range of NEFA concentrations. $\blacktriangle$, euthyroid rats; $\triangle$, hyperthyroid rats. Regression analysis yielded the following equations: euthyroid rats, $y = 11.0 + 85.4x$ ($r = 0.86$); hyperthyroid rats, $y = 27.7 + 122x$ ($r = 0.82$). Statistical analysis demonstrated a significant ($P < 0.001$) difference in the slopes of the two lines.

found in hyperthyroidism, the normal reciprocal relationship between rates of hepatic lipogenesis and long-chain-acylcarnitine formation was not observed: formation of long-chain acylcarnitine was increased, despite a doubling of the lipogenic rate relative to that of the controls (Tables 2 and 3). It is inferred that fat synthesis and mitochondrial fat oxidation can occur concurrently at high rates in hyperthyroid-rat liver *in vivo*.

Fate of acetyl-CoA after re-feeding

In starvation, utilization of oxaloacetate for gluconeogenesis [28] and a more reduced mitochondrial redox state [29] make oxaloacetate limiting for citrate synthesis. This restricts acetyl-CoA disposal via the tricarboxylic acid cycle and increases ketogenesis through an increased acetyl-CoA supply. Mean hepatic 3-hyperthyroid rats. This is consistent with increased ratios after re-feeding are shown in Table 2, and citrate concentrations in Table 3. At 1–2 h after glucose administration to euthyroid rats, [B]/[A] ratios were similar to those in the fed state (Table 2), whereas citrate concentrations were significantly increased relative to both starved (Table 3; see [30]) and fed ($0.22 \pm 0.03 \mu\text{mol/g wet wt.}$) values. There is compelling evidence (for review, see [31]) for continued gluconeogenesis after re-feeding, and, in support of this, inhibition of oxaloacetate utilization for gluconeogenesis with MPA resulted in additional increases in citrate concentrations (Table 3).

There was a significant effect of hyperthyroidism to decrease the [B]/[A] ratio at 0.5 h after re-feeding only. Citrate concentrations after glucose re-feeding were unaffected by hyperthyroidism. As citrate is not a metabolic end product, the interpretation of changes in citrate concentrations is difficult; nonetheless, as citrate concentrations are unchanged while, simultaneously and equally, long-chain acylcarnitine is increased and ketone bodies are decreased, it is concluded that either hyperthyroidism stimulates citrate disposal or acetyl-CoA derived from β -oxidation is utilized other than for citrate or acetoacetate formation. Very high citrate concentrations were achieved after MPA administration to hyperthyroid rats. This is consistent with increased pyruvate carboxylation [18]. The decreased citrate concentrations after glucose administration to MPA-treated hyperthyroid rats (Table 3) suggests diminished oxaloacetate availability and/or increased citrate disposal. Analogous decreases in citrate were not observed in response to glucose in MPA-treated euthyroid controls.

Lipogenic substrates after re-feeding

Previous work [11] has demonstrated that, as inhibition of ATP citrate lyase does not inhibit lipogenesis after glucose re-feeding of euthyroid or hyperthyroid rats, citrate is not the lipogenic substrate. In hyperthyroid rats, hepatic PDH remained inactive during the period when increases in lipogenesis were observed (Table 3), eliminating the possible use of carbohydrate as precursors. The results are consistent with the idea [11] that acetyl groups generated via β -oxidation in the mitochondria, but transported from the mitochondria other than as citrate, may ultimately provide the carbon for lipogenesis.

It is generally considered (see, e.g., [6]) that it is the lipogenic capacity of the liver which limits fatty acid synthesis after re-feeding. In the present experiments, rates of lipogenesis similar to or exceeding those found in the fed state were observed in rats treated with MPA and glucose, suggesting that other factors are involved. There was no correlation between the rate of lipogenesis and either PDH activity or citrate concentrations, at least during the time scale of the present experiments. Other factors such as the availability of cytoplasmic acetyl-CoA, NADPH or long-chain acyl-CoA (an allosteric

inhibitor of acetyl-CoA carboxylase) may assume regulatory importance.

General discussion

The salient findings of the present study are as follows:

(i) In the first 2 h after glucose re-feeding, the liver remains in the ketogenic mode. Mitochondrial β -oxidation of fatty acid is not immediately suppressed. Acetyl-CoA produced by β -oxidation is used for both ketone-body and citrate synthesis. The diversion of a proportion of acetyl-CoA into the ketogenic pathway implies an imbalance between oxaloacetate and acetyl-CoA availability. There is good evidence that gluconeogenesis from oxaloacetate continues after re-feeding, and this may contribute to the relative deficiency of oxaloacetate. Evidence for this in euthyroid rats is that MPA increases citrate concentrations after glucose re-feeding. The continued mitochondrial oxidation of fatty acids may be important in two respects. First, it may contribute to the hepatic energy supply under conditions where glycolysis and pyruvate oxidation are restricted, and second, it may ensure that acetyl-CoA is present in the mitochondria at concentrations sufficient to allow continued flux through pyruvate carboxylase.

(ii) Hyperthyroidism was demonstrated to increase flux through CPT 1, even at the very low NEFA concentrations (and by implication acyl-CoA concentrations; see [30]) observed after re-feeding. Previous work has demonstrated that the affinity of CPT 1 for acyl-CoA decreases during starvation [24], and it will be of interest to determine whether the effect of hyperthyroidism is simply a consequence of increased maximal activity of CPT 1, or whether an additional change in affinity for acyl-CoA is involved. There is no evidence that increased formation of acylcarnitine in hyperthyroidism is associated with decreased esterification: Laker & Mayes [32] have shown that plasma very-low-density-lipoprotein triacylglycerol does not change markedly *in vivo* in hyperthyroid rats. Consequently, it might be expected that the decreases in the cytoplasmic concentration of long-chain acyl-CoA which are normally observed during the first 2 h after glucose administration [30] would be achieved more rapidly in hyperthyroid than in euthyroid rats. This may have implications for the control of lipogenesis after re-feeding (see above).

(iii) Thyroid hormone has an intramitochondrial action to divert acetyl-CoA from ketogenesis. From the present experiments, it cannot be adduced whether this is achieved by acceleration of acetyl-CoA disposal by an alternative pathway (such as oxidation in the tricarboxylic acid cycle or the formation of acetylcarnitine [11]) or via a direct effect on the activities of one or more enzymes of the hydroxymethylglutaryl-CoA cycle.

Previous work has demonstrated that hyperthyroidism has profound effects on hepatic carbohydrate metabolism after re-feeding. The present study demonstrates additional effects on fatty acid disposal.

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