Liver carnitine metabolism after partial hepatectomy in the rat

Effects of nutritional status and inhibition of carnitine palmitoyltransferase

Paul S. Schofield, Timothy J. French*, Anthony W. Goode* and Mary C. Sugden+

*Department of Chemical Pathology, The London Hospital Medical College, Turner Street, London E1 2AD, and *The Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, England*

Received 20 March 1985

This study examined the effects of partial hepatectony on hepatic carnitine and acylcarnitine concentrations in fed or 24 h-starved partially hepatectonized (PH) or sham-operated (SO) rats at 1 or 4 days after surgery. The ratio of free to esterified carnitine was low in fed PH rats at day 1: the low ratio was increased to the SO value when mitochondrial fat oxidation was inhibited by 2-tetradecylglycidate. Starvation (24 h) increased plasma [non-esterified fatty acid] in PH or SO rats, the increases being greater at day 1 than at day 4. Hepatic [long-chain acylcarnitine] were also increased. These latter increases were a consequence of increased mitochondrial fat oxidation since they were not observed in PH or SO rats treated with 2-tetradecylglycidate. Whereas the starvation-induced increase in long-chain acylcarnitine was associated with increased [ketone body] in livers of SO rats at both day 1 and day 4 after surgery, [ketone body] was inappropriately low for the steady-state long-chain [acylcarnitine] in livers of PH rats at the first post-operative day. This was not a consequence of a decrease in [total carnitine] in the liver. The results are discussed with reference to the role of the liver in determining the relative proportions of the fat fuels available for extrahepatic tissues and the effects of liver cell proliferation on hepatic triacylclycerol metabolism.

Partial hepatectomy *Mitochondrial fat oxidation* *CPT 1* *2-Tetradecylglycidate* *Ketone bodies*

1. INTRODUCTION

The transport of long-chain acyl residues across the mitochondrial membrane is catalysed by carnitine palmitoyltransferases I and II (EC 2.3.1.21) [1]. The rate-limiting component of the transfer system is thought to be the outer acyltransferase (carnitine palmitoyl)transferase I; CPT 1 [2], which is found only in mitochondria (see [1]). The product of the CPT 1 reaction is long-chain acylcarnitine. Carnitine is also found in tissues as free (non-esterified) carnitine and as short-chain acylcarnitine. The proportion of total carnitine present as free carnitine depends on the nutritional and hormonal status, being decreased by starvation and diabetes, conditions associated with increased lipolysis [3].

Carnitine is present in dietary components and can also be synthesised de novo. The last step in the biosynthetic pathway is the hydroxylation of butyrobetaine which in the rat occurs only in the liver (see [1]). When dietary carnitine is not available hepatic biosynthesis must therefore provide for the carnitine requirements of both the liver and extra-hepatic tissues. Partial hepatectomy does not decrease tissue carnitine concentrations in rats starved for up to 2 days after surgery [4], indicating that carnitine biosynthesis in the regenerating liver is stringently linked to tissue requirements for this essential co-factor. However, a decrease in the proportion of hepatic carnitine pre-

+ To whom correspondence should be addressed

Published by Elsevier Science Publishers B.V. (Biomedical Division)
00145793/85/$3.30

sent as free (non-esterified) carnitine is observed [4].

The aims of this study were firstly to determine whether the change in ratio of free to esterified carnitine associated with partial hepatectomy is solely a consequence of a change in fatty acid availability, or whether it is related to liver cell proliferation, and secondly to investigate whether increased hepatic acylcarnitine concentrations reflect a change in mitochondrial fat metabolism. To these ends we examined the effects of partial hepatectomy on hepatic carnitine and acylcarnitine concentrations in partially hepatectomised (PH) or sham operated (SO) rats at 1 or 4 days after partial hepatectomy. Normally mitosis occurs at about 24 h after partial hepatectomy and by the fourth day substantial regeneration has occurred although the liver cell mass is not completely restored [5]. Because in unoperated rats alterations in nutritional state affect the proportion of the total carnitine present as carnitine esters, hepatic carnitine metabolism was examined both in rats fed ad libitum and rats starved for the 24 h immediately prior to sampling. In some experiments the mitochondrial uptake of long-chain acyl groups was inhibited by the administration of 2-tetradecylglycidic acid (TDG) which specifically inhibits CPT 1 [6]. This indirect approach to the elucidation of possible changes in mitochondrial carnitine metabolism was necessitated because in order to prevent changes in the proportion of free to acylated carnitines the tissue has to be rapidly frozen to the temperature of liquid nitrogen [3]. As freezing destroys the cell structure, mitochondrial and cytosolic intermediates cannot be separated by conventional fractionation techniques. Hepatic ketone body concentrations were also measured, the ketone bodies (3-hydroxybutyrate and acetoacetate) being the major products of mitochondrial β-oxidation in the liver. In livers of fed rats both regulation of CPT 1 and the hepatic concentration of carnitine are considered to be important in the control of ketogenesis (see [2]).

2. EXPERIMENTAL

2.1. *Materials*

Sources of materials were as described in [7]. The NEFA c-test kit for estimation of plasma non-esterified fatty acids was from Alpha Laboratories, Eastleigh, England. TDG (McN-3802) was generously provided by Ms M. Ralston, McNeill Pharmaceuticals, PA, USA.

2.2. *Methods*

Female albino Wistar rats (180–220 g) were subjected to a 12 h light/12 h dark cycle (light period started at 08.30 h). Rats were fed ad libitum prior to partial hepatectomy (removal of two-thirds of the liver as described in [8]) or sham operation. Following surgery, rats were either fed ad libitum or starved (grid-bottomed cages) for the 24 h immediately prior to sampling at day 1 or day 4 after surgery. Water was supplied ad libitum. Food intake was decreased during the first day after partial hepatectomy or sham operation [to 47 ± 4 (10)% and 84 ± 7 (8)%, respectively, of the control (unoperated) intake of 21.3 ± 2.1 g/day], but the operated rats were eating and growing normally by day 4.

Rats were administered water (control 1 ml/100 g body wt) or TDG [2.5 mg/100 g body wt, suspension in 0.5% (w/v) carboxymethylcellulose] intragastrically under light ether anaesthesia [9], and were killed 3 h later. Administration of carboxymethylcellulose or water did not significantly affect the parameters under investigation. Portions of liver were removed and immediately freeze-clamped in liquid N_2 whilst the rats were anaesthetised with sodium pentobarbital (60 mg/kg body wt). This procedure minimises changes in tissue carnitine profiles due to ischaemia (see [3]). The frozen liver was ground to a powder at −40°C and assayed for free and acylated carnitine in $HClO_4$ extracts as described in [10]. Free (non-esterified) carnitine was taken to be the carnitine found when $HClO_4$ extracts were examined without prior exposure to alkali. $HClO_4$-insoluble carnitine content was assumed to be long-chain esters (chain length > 10 carbon atoms), and the $HClO_4$-soluble fraction was assumed to contain short-chain derivatives and free carnitine (see [10]). KOH-neutralised $HClO_4$ extracts of frozen liver powder were used for the determination of total ketone body (3-hydroxybutyrate + acetoacetate) concentration [11]. Arterial blood samples were obtained and assayed for non-esterified fatty acids (plasma) and metabolites (KOH-neutralised $HClO_4$ supernatants).

Statistical significance of differences was as-

Table 1

Liver weight changes after partial hepatectomy or sham-operation in fed or 24 h-starved rats

	Fed ad libitum			
	Sham operation		Partial hepatectomy	
Time after surgery (d):	1	4	1	4
Wt liver removed (g/100 g rat)	–	–	2.43 ± 0.14	2.13 ± 0.12
Projected wt of liver remaining after resection (g/100 g rat)	4.28 ± 0.14	4.28 ± 0.14	1.85 ± 0.14[c]	2.15 ± 0.12[c]
Wt of liver at time of sampling (g/100 g rat)	3.43 ± 0.09	3.32 ± 0.22	1.51 ± 0.14[c]	2.61 ± 0.18[a]
Change in liver wt since resection (g/100 g rat)	−0.86 ± 0.09	0.96 ± 0.22	−0.35 ± 0.19[a]	0.47 ± 0.26[b]
n	8	7	6	7
	24 h-starved			
	Sham operation		Partial hepatectomy	
Time after surgery (d):	1	4	1	4
Wt liver removed (g/100 g rat)	–	–	2.38 ± 0.06	2.42 ± 0.07
Projected wt of liver remaining after resection (g/100 g rat)	4.28 ± 0.14	4.28 ± 0.14	1.90 ± 0.06[c]	1.86 ± 0.07[c]
Wt of liver at time of sampling (g/100 g rat)	2.92 ± 0.11[d]	3.24 ± 0.15	1.28 ± 0.05[c]	2.46 ± 0.07[c]
Change in liver wt since resection (g/100 g rat)	−1.36 ± 0.11[d]	1.04 ± 0.15	0.63 ± 0.06[c]	0.59 ± 0.08[c]
n	4	7	6	7

For details see section 2. Partially hepatectomised or sham-operated rats were either fed ad libitum or starved for the 24 h prior to sampling at 1 or 4 days after surgery. Statistically significant effects of partial hepatectomy are shown by: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$. Statistically significant effects of starvation are shown by: [d] $p < 0.01$

sessed by Student's unpaired *t*-test. Results are given as mean ± SE for the numbers of rats (*n*) specified.

3. RESULTS AND DISCUSSION

3.1. *Liver weight changes*

Table 1 shows the liver weights of fed or 24 h-starved PH or SO rats at 1 or 4 days after surgery. Immediately after partial hepatectomy the calculated weight of the portion of liver remaining was 43–50% that of the SO controls. In PH rats fed ad libitum, liver weights were 44 or 79% those of the SO controls at 1 or 4 days after surgery. Thus the liver mass was not increased during the first day after partial hepatectomy, but an approximate doubling of liver mass had occurred by day 4. A similar pattern of liver growth was observed for PH rats starved for the 24 h immediately prior to sampling. Sham operation itself resulted in a decrease in liver weight, which was apparent at 1 or 4 days after surgery in both fed and 24 h-starved rats.

3.2. *Plasma fatty acids and hepatic carnitine concentrations in fed rats*

Although plasma concentrations of non-esterified fatty acids (NEFA) were similar in fed SO rats at 1 or 4 days after surgery, plasma [NEFA] were relatively increased in PH rats after the first compared to the fourth post-operative day (table 2). The increased [NEFA] indicates an imbalance between the rates of NEFA production and utilisation in PH rats. An increased [NEFA]

Table 2

Effects of partial hepatectomy and 2-tetradecylglycidate on plasma concentrations of non-esterified fatty acids (NEFA) and hepatic concentrations of free and esterified carnitine in fed or 24 h-starved rats

Time after operation	Nutritional status	Treatment	n	Blood [NEFA] (mM)	[Liver carnitine] (nmol/g wet wt)			Free carnitine/ esterified carnitine
					Free	Esterified	Total	
1 day	Fed ad libitum	PH	6	0.45 ± 0.07^{a}	208.3 ± 43.5	332.6 ± 41.2	540.9 ± 66.8	0.65 ± 0.15
		SO	8	0.23 ± 0.03	260.1 ± 38.8	277.6 ± 19.3	524.1 ± 49.7	0.86 ± 0.10
		PH + TDG	5	0.81 ± 0.12^{cd}	278.3 ± 31.3	235.6 ± 41.2	514.2 ± 58.7	1.22 ± 0.13^{d}
		SO + TDG	5	0.13 ± 0.02^{d}	298.6 ± 41.3	255.3 ± 14.5	553.9 ± 54.2	1.15 ± 0.11
	24 h-starved	PH	7	1.01 ± 0.08^{ci}	91.9 ± 12.4^{b}	316.6 ± 32.1	408.5 ± 42.2	0.29 ± 0.03^{ag}
		SO	4	0.45 ± 0.04^{h}	186.7 ± 24.4	269.7 ± 29.5	456.4 ± 35.3	0.72 ± 0.13
		PH + TDG	6	1.62 ± 0.05^{fi}	360.9 ± 25.0^{f}	373.0 ± 30.7^{g}	724.6 ± 42.3^{fg}	1.02 ± 0.12^{f}
		SO + TDG	6	1.42 ± 0.10^{fi}	443.6 ± 37.2^{fg}	366.1 ± 12.4^{di}	809.6 ± 29.3^{fh}	1.23 ± 0.12^{d}
4 days	Fed ad libitum	PH	7	0.29 ± 0.09	214.3 ± 19.8	265.8 ± 20.4	480.1 ± 34.9	0.82 ± 0.06
		SO	7	0.20 ± 0.04	224.2 ± 35.9	250.7 ± 18.8	475.0 ± 49.4	0.89 ± 0.11
		PH + TDG	5	0.21 ± 0.11	216.9 ± 11.8	235.4 ± 16.0	452.3 ± 8.8	0.96 ± 0.13
		SO + TDG	5	0.11 ± 0.02	207.7 ± 30.6	195.3 ± 17.7	403.1 ± 36.4	1.05 ± 0.12
	24 h-starved	PH	7	0.37 ± 0.06	154.5 ± 16.0^{dg}	479.8 ± 44.8^{ai}	634.3 ± 59.7^{g}	0.32 ± 0.02^{ai}
		SO	7	0.34 ± 0.03^{g}	163.4 ± 15.8	338.5 ± 22.8^{g}	501.9 ± 17.8	0.51 ± 0.07^{g}
		PH + TDG	5	1.37 ± 0.09^{fi}	455.6 ± 49.4^{fh}	322.1 ± 25.5^{dg}	777.7 ± 72.5^{h}	1.40 ± 0.06^{fg}
		SO + TDG	5	1.11 ± 0.13^{fi}	356.7 ± 20.2^{fh}	290.8 ± 25.6^{h}	524.2 ± 50.7	1.24 ± 0.06^{f}

For details see section 2. Rats were subjected to partial hepatectomy (PH) or sham-operation (SO) and either fed ad libitum or starved for 24 h prior to sampling at 1 or 4 days after surgery. TDG was administered by intragastric intubation 3 h prior to sampling. Statistically significant effects of partial hepatectomy compared with sham-operation are shown by: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$. Statistically significant effects of TDG are shown by: [d] $p < 0.05$; [e] $p < 0.01$; [f] $p < 0.001$. Statistically significant effects of starvation are shown by: [g] $p < 0.05$; [h] $p < 0.01$; [i] $p < 0.001$

was also observed when mitochondrial long-chain fatty acid uptake was blocked by TDG, i.e., when mitochondrial fat utilisation was inhibited. This demonstrates that at least part of the increase in NEFA in fed PH rats at 24 h after surgery is due to accelerated adipose tissue lipolysis. TDG treatment did not increase [NEFA] in fed SO rats at either 1 or 4 days after surgery or in PH rats at 4 days after surgery, which is indicative of low rates of lipolysis in these groups. It is interesting that although food intake was decreased in both PH and SO rats during the first post-operative day, lipolysis is stimulated only in the former group. This presumably reflects the increased stress associated with partial hepatectomy.

The increase in plasma [NEFA] observed at 24 h after partial hepatectomy, somewhat surprisingly, was not associated with marked changes in hepatic concentrations of free or esterified carnitine (table 2). However, a disturbance in hepatic fat metabolism was suggested by the accumulation of lipid in the liver remnant, the lipid contents of the fed PH or SO livers expressed on a wet weight basis being 76.6 ± 5.8 (5) or 35.3 ± 2.5 (5) mg/g, respectively, at 1 day after surgery. The relatively low ratio of free to esterified carnitine in livers of fed PH rats on the first day after partial hepatectomy was increased by the administration of TDG. As [total carnitine] was unchanged by TDG treatment, it can be inferred that the increase is due to a net increase in mitochondrial acylcarnitine formation. This could arise either because of increased activity of CPT 1 in the direction of acylcarnitine formation or because of impaired utilization of acylcarnitine. The concentrations of free and esterified carnitine in livers of fed PH or

SO rats were similar by 4 days after surgery.

3.3. *Plasma fatty acids and hepatic carnitine concentrations in 24 h-starved rats*

Starvation of either PH or SO rats increased NEFA concentrations in plasma sampled at 1 day after surgery by 124 or 96%, respectively (table 2). This increase was associated with decreases in [free carnitine] and the ratio of free to esterified carnitine in the livers of PH rats. There were no significant changes in [free carnitine] in the SO rats, or esterified or total concentrations in the PH or SO rats. By the fourth day after surgery, although increases in plasma NEFA in response to 24 h starvation were relatively modest, there were marked decreases in the ratios of free to esterified carnitine in the livers of both PH and SO rats. These differences in the responses to starvation at the first and fourth post-operative days demonstrate that surgical stress has an acute effect on hepatic acylcarnitine metabolism, and possibly fatty acid turnover. Plasma [NEFA] in starved TDG-treated rats (PH and SO) were greater than in fed TDG-treated rats, indicating that both PH and SO rats respond to food deprivation with increased adipose tissue lipolysis. It is also of interest that [NEFA] were similar in starved, PH rats at 1 day and 4 days after surgery if the rats were administered TDG (see table 3), but not if the rats were untreated (concentrations of 1.01 ± 0.08 (7) and 0.37 ± 0.06 (7), respectively, at days 1 and 4, see table 2). This indicates that decreased NEFA utilization in PH rats as well as increased lipolysis (see above) can contribute to the elevation in [NEFA] observed at 24 h after surgery. It is likely that the decreased NEFA utilization relates, at least in part, to the decreased liver mass. These results emphasise the importance of the liver as a site of NEFA utilization. The ratio of free to esterified carnitine was increased by TDG in starved rats at 24 h after surgery, but this effect of TDG was not associated with a decrease in esterified carnitine in either PH or SO rats, an unexpected result in view of the action of TDG to in-

Table 3

Effects of partial hepatectomy and 2-tetradecylglycidate on hepatic concentrations of short-chain and long-chain acylcarnitines and ketone bodies in fed or 48 h-starved rats

Time after operation	Nutritional status	Treatment	*n*	Short-chain acylcarnitine (nmol/g wet wt)	Long-chain acylcarnitine (nmol/g wet wt)	Total ketone bodies (μmol/g wet wt)
1 day	Fed ad libitum	PH	6	298.3 ± 34.0	34.3 ± 4.7[a]	0.65 ± 0.02
		SO	8	243.5 ± 20.8	20.5 ± 1.9	0.52 ± 0.10
		PH + TDG	5	222.2 ± 30.2	13.7 ± 2.1[e]	0.58 ± 0.03
		SO + TDG	5	239.4 ± 14.2	15.9 ± 4.6	0.60 ± 0.07
	24 h-starved	PH	7	259.3 ± 29.5	57.2 ± 7.8[ag]	0.65 ± 0.05[b]
		SO	4	234.9 ± 26.5	34.8 ± 4.1[g]	1.05 ± 0.08[h]
		PH + TDG	6	336.3 ± 27.0[g]	28.3 ± 4.0[cg]	0.56 ± 0.05
		SO + TDG	6	337.5 ± 12.7[ei]	28.4 ± 1.5[g]	0.57 ± 0.03[f]
4 days	Fed ad libitum	PH	7	243.4 ± 18.8	22.4 ± 2.5	0.47 ± 0.05
		SO	7	230.3 ± 17.6	20.4 ± 2.7	0.55 ± 0.08
		PH + TDG	5	223.6 ± 16.3[a]	11.8 ± 1.5[e]	0.24 ± 0.03[he]
		SO + TDG	5	177.7 ± 5.0[d]	17.6 ± 3.0	0.37 ± 0.01[d]
	24 h-starved	PH	7	428.5 ± 35.6[ai]	35.7 ± 10.0[g]	0.96 ± 0.08[i]
		SO	7	311.0 ± 22.5[g]	27.5 ± 2.6	1.07 ± 0.19[g]
		PH + TDG	5	287.9 ± 16.2[cg]	34.2 ± 7.8[g]	0.35 ± 0.05[bf]
		SO + TDG	5	265.0 ± 27.9[g]	25.8 ± 3.4	0.66 ± 0.05[i]

For details see section 2 and the legend to table 2. Statistically significant effects of partial hepatectomy are shown by: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$. Statistically significant effects of TDG are shown by: [d] $p < 0.05$; [e] $p < 0.01$; [f] $p < 0.001$. Statistically significant effects of starvation are shown by: [g] $p < 0.05$; [h] $p < 0.01$; [i] $p < 0.001$

hibit CPT 1. The major effect of TDG was to cause a marked increase in [free carnitine], and consequently total carnitine was increased. TDG also increased free (and total) carnitine in 24 h-starved PH and SO rats at the fourth post-operative day. Others have shown that in suckling rats, the chronic administration of TDG can increase [free carnitine] in the liver [12]. Since in the present study TDG increased hepatic carnitine concentrations only if the rats were starved, it is implied that the control of liver carnitine concentration is linked to a requirement for hepatic fat oxidation. Interestingly, although the first day after surgery was associated with a decreased food intake in both PH and SO rats, there was no tendency for TDG to increase hepatic [carnitine].

3.4. *Mitochondrial acylcarnitine and ketone body formation in fed or starved rats*

Table 3 shows the distribution of esterified carnitine between short-chain and long-chain acylcarnitine, and total ketone body concentrations in livers of PH and SO rats. [Long-chain acylcarnitine] was significantly increased in livers of fed rats at day 1 after partial hepatectomy, but the increases were not found if the rats were administered TDG indicating that they were due to increased [long-chain acylcarnitine] in the mitochondrial compartment. There were further increases in the steady-state [long-chain acylcarnitine] in livers of PH rats in response to starvation. Starvation also increased [long-chain acylcarnitine] in SO rats at the first post-operative day. Whereas the starvation-induced increase in long-chain acylcarnitine was associated with increased [ketone body] in livers of SO rats, the ketone body concentration was inappropriately low for the steady-state [long-chain acylcarnitine] in livers of PH rats.

By the fourth day after partial hepatectomy, the hepatic [long-chain acylcarnitine] and [ketone body] were similar in the PH or SO groups. Effects of starvation to increase [long-chain acylcarnitine] in livers of PH rats were less marked than at day 1, consistent with less dramatic increases in NEFA response to starvation (table 2). [Long-chain acylcarnitine] were similar in starved SO rats at the first and fourth post-operative days, as were [ketone body]. Acid-insoluble carnitines are the product of the CPT 1 reaction. If CPT 1 were rate-limiting for ketogenesis, as suggested by McGarry and Foster (see [2]) increased velocity of the reaction in starvation would lead both to an increased steady-state concentration of long-chain acylcarnitines and to increased ketogenesis. Although the parallel increases in response to starvation in SO rats at 1 and 4 days after surgery and in PH rats at 4 days after surgery might therefore be taken to indicate a regulatory role for CPT 1, TDG decreased liver [ketone body] without significant decreases in long-chain acylcarnitine in these groups of rats (see table 3). This suggests that although the accumulation of mitochondrial long-chain acylcarnitine in response to starvation may be due in part to increased CPT 1 activity, the mitochondrial utilization of long-chain acyl groups esterified to carnitine is determined by the flux through a step after CPT 1. This may be the CPT II reaction which has been shown by others [13] to be increased in starvation. A rate-limiting step after CPT 1 might also explain why in starved PH rats at day 1 after surgery increases in [long-chain acylcarnitine] are not associated with increased [ketone body], and effects of TDG to decrease [long-chain acylcarnitine] do not lead to decreased [ketone body]. Flux rates were not measured in the present study and therefore it cannot be excluded that in livers of PH rats there is also increased complete oxidation of acetyl-CoA to CO_2 at the expense of ketogenesis. Nakatani and co-workers [14–16] have suggested that fatty acids are important fuels for the liver remnant in the first 24 h after partial hepatectomy. Alternatively, in PH rats the rate of peripheral oxidation of the ketone bodies may exceed the rate of ketone body production by the decreased liver mass, even though the rate of ketogenesis per unit weight of liver may be increased. The present results do however exclude the possibility that the decreased hepatic [ketone body] is due to a decreased [carnitine] secondary to impaired biosynthesis.

In summary, the present results indicated that the decreases in hepatic ratios of free to esterified carnitine observed at 1 day after partial hepatectomy are predominantly due to increased mitochondrial [acylcarnitine]. The changes are probably unrelated to liver cell proliferation (since the size of the liver is not increased over the first post-operative day) but instead are likely to result from increased NEFA availability, plasma [NEFA]

being elevated both because of increased adipose tissue lipolysis and decreased hepatic utilization of NEFA. The disturbances in hepatic carnitine metabolism are not evident by the fourth day after partial hepatectomy by which time liver mass has greatly increased. Liver [ketone body] are low in starved PH rats at day 1 after partial hepatectomy, despite increased mitochondrial [acylcarnitine] and unchanged [total carnitine]. The results therefore demonstrate the important role of the liver in determining the relative proportions of fat fuels (viz. NEFA ketone bodies) available for extrahepatic tissues.

ACKNOWLEDGEMENTS

This work was supported by a project grant from the UK Medical Research Council. We thank Mrs Elaine Davis for expert secretarial assistance.

REFERENCES

[1] Bremer, J. (1983) Physiol. Rev. 63, 1420–1480.
[2] McGarry, J.D. and Foster, D.W. (1980) Annu. Rev. Biochem. 49, 395–420.
[3] Pearson, D.J. and Tubbs, P.K. (1967) Biochem. J. 105, 953–963.
[4] French, T.J., Goode, A.W., Schofield, P.S. and Sugden, M.C. (1985) Biosci. Rep. 5, 47–55.
[5] Gove, C.D. and Hems, D.A. (1978) Biochem. J. 170, 1–8.
[6] Tutwiler, G.F. and Dellevigne, P. (1979) J. Biol. Chem. 254, 2935–2941.
[7] Sugden, M.C., Watts, D.J. and Marshall, C.E. (1982) Biochem. J. 204, 749–756.
[8] Higgins, G.M. and Anderson, R.M. (1831) Arch. Pathol. 12, 186–202.
[9] Tutwiler, G.F., Mohrbacher, R. and Ho, W. (1979) Diabetes 28, 242–248.
[10] Brass, E.P. and Hoppel, C.L. (1978) J. Biol. Chem. 253, 2688–2693.
[11] Williamson, D.H., Mellanby, J. and Krebs, H.A. (1962) Biochem. J. 82, 90–96.
[12] Frost, S.C. and Wells, M.A. (1982) Biochem. J. 204, 861–863.
[13] Zammit, V.A. (1980) Biochem. J. 190, 293–300.
[14] Nakatani, T., Yasuda, K., Ozawa, Z., Kawashima, S. and Tobe, T. (1982) Clin. Sci. 62, 295–297.
[15] Nakatani, T., Ozawa, Z., Asano, M., Ukikusa, M., Kamiyama, Y. and Tobe, T. (1981) J. Lab. Clin. Med. 97, 877–898.
[16] Nakatani, T., Ozawa, Z., Asano, M., Ukikusa, M., Kamiyama, Y. and Tobe, T. (1981) Life Sci. 28, 257–264.