Ketone-body metabolism after surgical stress or partial hepatectomy

Evidence for decreased ketogenesis and a site of control distal to carnitine palmitoyltransferase I

Paul S. SCHOFIELD, Timothy J. FRENCH and Mary C. SUGDEN*

Department of Chemical Pathology, London Hospital Medical College, Turner Street, London E1 2AD, U.K.

Rats were subjected to laparotomy, or laparotomy and partial hepatectomy, at 0–48 h before administration of water or medium-chain-length triacylglycerol, having been starved post-operatively. Functional hepatectomies were performed at intervals after the intragastric load. Blood ketone-body concentrations after medium-chain triacylglycerol administration and/or functional hepatectomy of these rats were compared with values obtained in starved control rats. Decreased ketonaemia in response to medium-chain triacylglycerol was observed for up to 48 h after partial hepatectomy and at 1 and 2 h after laparotomy, but not at 24 or 48 h after laparotomy. Rates of ketone-body clearance after functional hepatectomy were unaffected by prior laparotomy or partial hepatectomy. Ketonaemia after medium-chain-triacylglycerol administration was only partially blocked by inhibition of CPT I (carnitine palmitoyltransferase I). The results demonstrate sustained effects of partial hepatectomy and short-term effects of surgical stress to decrease ketonaemia via inhibition of ketogenesis at site(s) distal to CPT I.

INTRODUCTION

The increased rate of ketogenesis observed on the transition from the fed to the starved state results both from increased fatty acid supply (secondary to increased lipolysis) and diversion of long-chain acyl-CoA from esterification to mitochondrial β -oxidation (reviewed in [1]). One physiologically important regulatory mechanism is the modulation of flux through carnitine palmitoyltransferase I (EC 2.3.1.21; CPT I) by malonyl-CoA, an intermediate of lipogenesis, whose concentration reflects hepatic carbohydrate status. At the low rates of lipogenesis found in starvation, decreased malonyl-CoA concentrations permit the diversion of long-chain fatty acid into oxidative pathways in the mitochondria. CPT I is also inhibited by fatty acid analogues such as 2-tetradecylglycidate (TDG), inhibition occurring via formation of the CoA ester [2]. A second intrahepatic control mechanism involves the partitioning of intramitochondrial acetyl-CoA between ketogenesis and oxidation to CO_2 via the tricarboxylic acid cycle. This mechanism may be of particular importance under conditions where concentrations of acute-acting stress hormones (such as vasopressin, angiotensin and the catecholamines) are increased (see [1]).

When rats are subjected to partial hepatectomy and then starved, blood ketone-body concentrations are substantially less than those of unoperated or sham-operated controls [3]. Rates of lipogenesis [4] and esterification [5] are increased, suggesting possible restriction of ketogenesis by mitochondrial substrate supply. These changes, possibly accompanied by increased oxidation of acetyl-CoA to CO_2 [3,6], may be responsible for the decreased ketone-body concentrations. Previous experiments have not, however, indicated

which of these possible factors constitutes the major mechanism of control, nor have they excluded the possibility that decreased ketonaemia results from accelerated extrahepatic utilization of ketone bodies.

A second pathophysiological state associated with decreased ketonaemia is that of acute surgical stress or trauma [7]. An inverse relationship exists between the blood ketone-body concentration and the severity of injury [7], but again it is uncertain whether ketonaemia results from decreased hepatic ketone-body production or increased peripheral utilization. The anti-ketonaemic effects of trauma are mimicked experimentally by the administration of adrenaline [8]. In this instance, however, decreased ketonaemia is also observed after administration of medium-chain-length fatty acids, which are not esterified and whose mitochondrial metabolism is less dependent on the carnitine shuttle than is that of long-chain fatty acids (reviewed in [9]), suggesting increased peripheral ketone-body utilization or an intramitochondrial action of the hormone.

In the present experiments, we have utilized two approaches to elucidate the reason for decreased ketonaemia after surgical stress or partial hepatectomy. Firstly we have investigated the ketonaemic response to the administration of medium-chain triacylglycerol in normal (unoperated) rats and rats subjected to laparotomy or laparotomy and partial hepatectomy at various times before medium-chain-triacylglycerol administration. The objective of these experiments was to determine the importance of site(s) of control of ketogenesis distal to CPT I. Secondly, we have performed functional hepatectomies on laparotomized, partially hepatectomized or unoperated rats after medium-chain-triacylglycerol administration. The aim of these latter experiments was to establish whether in the

Abbreviations used: CPT I, carnitine palmitoyltransferase I; TDG, 2-tetradecylglycidate.

* To whom correspondence should be addressed.

former two groups, as in unoperated rats [10], the rate of ketone-body utilization is mainly determined by the degree of ketonaemia, and thus whether decreased blood ketone-body concentrations can be attributed to decreased ketogenesis.

MATERIALS AND METHODS

Materials

Sources of materials were as described in [8]. TDG (McN-3802) was generously provided by McNeil Pharmaceutical, PA, U.S.A.

Methods

Female albino Wistar rats (170–220 g) were subjected to a 12 h-light/12 h-dark cycle, and were used after 24 h or 48 h starvation in grid-bottomed cages. Fed rats were allowed free access to standard rodent diet. Water was supplied *ad libitum*.

Partial hepatectomy (comprising laparotomy and removal of two-thirds of the liver) or laparotomy (sham operation) was performed under diethyl ether anaesthesia as described previously [3,6]. Rats were starved for up to 48 h post-operatively. Unoperated rats were starved but not subjected to ether anaesthesia or surgery.

Experiments were started between 08:30 and 09:30 h. Medium-chain triacylglycerol (1.5 ml), TDG (2.5 mg/100 g body wt.) or water (1.5 ml) was administered intragastrically. The rats were anaesthetized (sodium pentobarbital, 6 mg/100 g body wt.) at intervals after the intragastric load, and blood (0.25 ml) was sampled from the anterior vena cava. Rats were then subjected to functional hepatectomy (by isolating the liver from the general circulation) as described in [11]. The decrease in blood ketone bodies after functional hepatectomy was monitored from 4 to 30 min, with sampling from the vena cava at 4, 7.5, 15 and 30 min. Rates of ketone-body disappearance were linear for the first 7.5 min after functional hepatectomy (see below). In some experiments ligatures were placed around the appropriate vessels, but not tied (see [11] for details): under these circumstances, ketone-body concentrations were unchanged after 7.5 min (results not shown). Serum and deproteinized blood samples were assayed for long-chain non-esterified fatty acids and metabolites as described previously [3,6].

Statistical analysis

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

RESULTS AND DISCUSSION

Ketone-body concentrations after medium-chain-triacylglycerol administration to fed or starved unoperated rats

Blood ketone-body concentrations were low in fed rats (Fig. 1), as would be expected from the limited availability of endogenous ketogenic substrate (non-esterified fatty acids). Starvation for 24 h caused a 5-fold rise in ketone-body concentrations. A small additional increase was observed when the period of starvation was extended to 48 h.

The time course for changes in blood ketone-body concentrations after administration of medium-chain

Fig. 1. Blood ketone-body concentrations after administration of medium-chain triacylglycerol to control (unoperated) rats

For details see the text. Medium-chain triacylglycerol (1.5 ml) was administered intragastrically to fed (■), 24 h-starved (▲) or 48 h-starved (●) unoperated rats. Results are shown as means $\pm$ S.E.M. for 6–12 rats.

triacylglycerol to unoperated rats is shown in Fig. 1. Taking into account the different rates of ketogenesis from non-esterified fatty acids, there was only a limited effect of nutritional status on the ketonaemic response to administration of triacylglycerol. Thus at 2 h after the intragastric load the response in starved rats was only approx. 1.5-fold greater than that in fed rats. This finding is consistent with previous observations (reviewed in [12]) that ketogenesis from medium-chain-length fatty acids is little affected by carbohydrate status because of low flux through CPT I. The administration of TDG to rats not given medium-chain-length triacylglycerol did not significantly affect blood ketone-body concentrations in fed rats, but decreased ketone-body concentrations to 'fed' values in starved rats [from 0.86 ± 0.08 (5) mM to 0.19 ± 0.02 (5) mM; 78%; $P < 0.001$; see also [2] and [13]–[15]]. In starved rats given medium-chain triacylglycerol, although TDG significantly decreased ketone-body concentrations [from 4.52 ± 0.33 (15) mM to 2.3 ± 0.47 (10) mM; 49%; $P < 0.001$], significant ketonaemia was still observed. In view of the rapid decline in ketonaemia observed when ketogenesis is blocked by functional hepatectomy (see below and [3] and [11]), the results suggest that although a proportion of the administered medium-chain-length triacylglycerol is metabolized via CPT I (see [9]), approx. 50% enters the mitochondria for oxidation independently of CPT I. TDG did not affect the rate of ketone-body disappearance after functional hepatectomy (results not shown), indicating that its anti-ketonaemic effect was achieved via inhibition of ketone-body production rather than acceleration of clearance.

Blood ketone-body concentrations after functional hepatectomy of unoperated starved rats are shown in Fig. 2(a). The rate of ketone-body clearance declined after 7.5 min, consistent with the idea that utilization

Fig. 2. Changes in blood ketone-body concentrations after functional hepatectomy of control rats

For details see the text. (a) Rate of decline of blood ketone-body concentrations after functional hepatectomy of 24 h-starved (▲) or 48 h-starved (●) rats. Results are shown as means $\pm$ S.E.M. for 6–12 rats. (b) Relationship between initial ketone-body concentrations and clearance rates, measured over the first 7.5 min in 24 h-starved (▲, △) or 48 h-starved (●, ○) rats given water (▲, ●) or medium-chain triacylglycerol (△, ○).

rates are proportional to blood concentrations (see [11]). Non-linearity was largely the result of a rapid decrease in acetoacetate, the preferred substrate in most tissues [12]; the rate of disappearance of 3-hydroxybutyrate was linear for up to 15 min. In subsequent experiments, rates of ketone-body disappearance were calculated for the initial 7.5 min period after functional hepatectomy and Fig. 2(b) shows that the rate of decline was indeed proportional to the initial ketone-body concentration. This relationship held not only in starved water-fed rats, but also in starved rats after administration of medium-chain triacylglycerol (see Fig. 2b).

Fig. 3. Blood ketone-body concentrations after administration of medium-chain triacylglycerol to starved rats at 24–48 h after laparotomy or laparotomy and partial hepatectomy

For details see the text. Medium-chain triacylglycerol (1.5 ml) was administered intragastrically to 24 h-starved (▲, △) or 48 h-starved (●, ○) rats subjected to laparotomy (▲, ●) or partial hepatectomy (△, ○) at the onset of starvation. Results are shown as means $\pm$ S.E.M. for 6–12 rats.

Ketone-body concentrations after medium-chain-triacylglycerol administration at 24 h or 48 h after laparotomy or laparotomy and partial hepatectomy

The time courses for the response of 24 h- and 48 h-starved rats subjected to laparotomy or laparotomy and partial hepatectomy at the onset of the period of starvation are shown in Fig. 3. A comparison of the ketone-body concentrations observed after medium-chain-triacylglycerol administration to starved unoperated rats (Fig. 1) or laparotomized rats (Fig. 3) indicates that laparotomy at 24 h or 48 h before sampling did not diminish the ketonaemic response. In marked contrast, partial hepatectomy at the onset of starvation dramatically decreased ketonaemia in response to medium-chain triacylglycerol. This effect of partial hepatectomy was greater when the operation was carried out at 24 h before triacylglycerol administration than when it was performed at 48 h before triacylglycerol administration. The significant increase in liver weight between 24 and 48 h after partial hepatectomy (Table 1) could contribute to the improved response, but the almost 2-fold difference in the responses of 48 h-starved rats subjected to laparotomy or laparotomy and partial hepatectomy (Fig. 3) cannot be ascribed solely to differences in liver mass (see Table 1).

Blood ketone-body concentrations after functional hepatectomy of starved rats subjected to laparotomy or laparotomy and partial hepatectomy at 24–48 h before sampling are shown in Fig. 4(a). The overall rates of decrease in the blood ketone-body concentrations in previously laparotomized rats given water or triacylglycerol were again proportional to initial ketone-body concentrations over the first 7.5 min after functional hepatectomy (Fig. 4b). There was no indication that ketone-body clearance, at a given level of ketonaemia, was increased compared with that observed in unoperated rats (Fig. 2b).

Acute effects of laparotomy or laparotomy and partial hepatectomy in the ketonaemic response to medium-chain triacylglycerol

To examine the direct effects of a decreased liver mass

Table 1. Liver weights after partial hepatectomy or sham operation (laparotomy)

For details see the text. Liver weights in fed unoperated rats were 4.35 ± 0.09 (15) g/100 g body wt. The surgical procedures were carried out at the onset of the period of starvation. Significant differences between liver weights after partial hepatectomy or sham operation are indicated: ** $P < 0.001$.

Surgical manipulation	Nutritional status . . .	Liver wt. (g/100 g body wt.)	
		24 h starved	48 h starved
None (unoperated controls)		3.60 ± 0.09 (19)	3.08 ± 0.08 (23)
Sham operation (laparotomy)		3.70 ± 0.07 (17)	3.33 ± 0.07 (16)
Partial hepatectomy		2.24 ± 0.06 (21)**	2.97 ± 0.06 (15)**

Fig. 4. Changes in blood ketone-body concentrations after functional hepatectomy of starved rats at 24–48 h after laparotomy or laparotomy and partial hepatectomy

For details see the text. (a) Rate of decline of blood ketone-body concentrations after functional hepatectomy of 24 h-starved ($\blacktriangle$, $\triangle$) or 48 h-starved ($\bullet$, $\circ$) rats subjected to laparotomy ($\blacktriangle$, $\bullet$) or laparotomy and partial hepatectomy ($\triangle$, $\circ$) at the onset of starvation. Results are shown as means $\pm$ S.E.M. for 7–12 rats. (b) Relationship between initial ketone-body concentrations and clearance rates, measured over the first 7.5 min in 24 h-starved ($\blacktriangle$, $\triangle$, $\blacksquare$, $\square$) or 48 h-starved ($\bullet$, $\circ$, $\blacksquare$, $\square$) laparotomized ($\blacksquare$, $\square$) or partially hepatectomized ($\triangle$, $\circ$) rats given water ($\blacktriangle$, $\triangle$, $\bullet$, $\circ$) or medium-chain triacylglycerol ($\blacksquare$, $\square$, $\blacksquare$, $\square$).

on the ketonaemic response to medium-chain-triacylglycerol administration, 24 h-starved rats were subjected to partial hepatectomy and then immediately given medium-chain triacylglycerol. Instead of the rise in ketone-body concentrations observed in unoperated rats (Fig. 1), an initial decline in ketone-body concentrations was observed [to 0.65 ± 0.14 (5) mM at 1 h after triacylglycerol administration]. Blood ketone-body concentrations at 2 h after triacylglycerol administration were also greatly decreased compared with unoperated controls [0.91 ± 0.17 (5) mM compared with 4.06 ± 0.45 (8) mM; $P < 0.001$]. The ketonaemic response in the corresponding sham-operated (laparotomized) rats were variable, and, although substantial elevations in blood ketone-body concentrations were observed, values were generally less than those observed in unoperated rats (results not shown). In a separate series of experiments we therefore specifically examined acute effects of laparotomy on the ketonaemic response; the results are shown in Table 2. Blood ketone-body concentrations after medium-chain-triacylglycerol administration were

substantially decreased in laparotomized rats. The anti-ketonaemic effect of surgical stress was most marked in the first hour after surgery, but was also apparent at 2 h. It was also observed in rats subjected to laparotomy at 1 h after intragastric administration, by which time intestinal absorption is essentially complete [13]. As with unoperated rats or rats sampled at 1 or 2 days after surgery, rates of disappearance of ketone bodies from the blood after functional hepatectomy were proportional to the initial ketone-body concentrations (see Fig. 5). It can therefore be concluded that, in the short term, surgery leads to decreased ketogenesis, and, since in the present series of experiments the ketogenic substrate was medium-chain triacylglycerol, a site of action distal to CPT I is strongly implied. It should be noted that the acute effects of partial hepatectomy on blood ketone-body concentrations were more marked than those of laparotomy alone, and even after the provision of additional substrate (medium-chain triacylglycerol) ketonaemia was decreased. The results suggest marked inhibition of ketogenesis after liver resection, but, in view

Table 2. Effects of acute surgical stress on the response to administration of medium-chain triacylglycerol

A venous blood sample was taken under diethyl ether anaesthesia immediately before laparotomy, which was performed either at the time of administration of triacylglycerol (groups 1-4) or at 1 h after administration of triacylglycerol (group 5). A second venous blood sample was taken at the time of killing (1 h after laparotomy). Blood ketone-body concentrations in rats not subjected to surgery are shown for comparison (group 6). In this group, samples taken at 0, 1 h and 2 h after intubation were from different rats. Statistically significant differences between laparotomized and control (group 5) rats are indicated: ***P* < 0.001.

Group	Treatment	Time of sampling (h after intubation) . . .	Ketone-body concn. (mM)			Change in concn. (% of 0 h value)
			0	1	2	
1.	Laparotomy and water intubation		1.42 ± 0.08 (6)	1.14 ± 0.13 (6)	—	-20 ± 7
2.	Laparotomy and water intubation		1.12 ± 0.07 (5)	—	1.12 ± 0.08 (5)	+2 ± 8
3.	Laparotomy and triacylglycerol intubation		1.21 ± 0.08 (6)	1.67 ± 0.14 (6)**	—	+40 ± 7
4.	Laparotomy and triacylglycerol intubation		1.27 ± 0.09 (6)	—	2.71 ± 0.20 (6)**	+118 ± 16
5.	Laparotomy at 1 h after triacylglycerol intubation		—	3.15 ± 0.30 (6)	1.96 ± 0.36 (6)**	-40 ± 6
6.	Triacylglycerol without laparotomy		1.20 ± 0.10 (12)	2.74 ± 0.29 (6)	4.06 ± 0.45 (8)	—

Fig. 5. Changes in blood ketone-body concentrations after functional hepatectomy of starved rats at 1 or 2 h after laparotomy or laparotomy and partial hepatectomy

For details see the text. The Figure indicates the relationship between initial ketone-body concentrations and clearance rates, measured over the first 7.5 min, in 24 h-starved (▲, △, ■, □) or 48 h-starved (●, ○, ■, □) rats given water (▲, △, ●, ○) or medium-chain triacylglycerol (■, □, ■, □) at the time of laparotomy (■, □) or laparotomy and partial hepatectomy (▲, ●).

of the more severe surgical stress, a direct relationship between liver weight (i.e. ketogenic capacity) and maintenance of ketonaemia cannot be adduced. Some insight into this was, however, provided by the experiments shown in Table 3, where the response to 48 h starvation was investigated at 2 days after partial hepatectomy or laparotomy, with sampling at day 4 post-operatively. No increase in liver mass was observed between days 2 and 4 post-operatively if the rats were starved. Although starvation-induced increases in non-esterified fatty acid concentrations were greater in rats starved for 48 h immediately after partial hepatectomy, increases in ketone-body concentrations were significantly less than in rats starved between days 2 and 4 after partial hepatectomy, despite similar liver weights. The results indicate that decreased ketonaemia after partial hepatectomy is not of necessity the consequence of a decreased liver mass. Instead it seems likely either to be specifically related to liver cell division, which occurs at 24-30 h after liver resection, or to be a response to recent severe surgical stress.

General discussion

Although some of the biochemical effects of trauma, including surgical trauma, have been well described (for review see [14]), relatively little attention has been directed towards possible changes in ketone-body metabolism. Lipolysis is increased, but there is often a failure to achieve the raised ketone-body concentrations consistent with the increased precursor supply. Whereas

Table 3. Long-term effects of partial hepatectomy or laparotomy on the ketonaemic response to 48 h starvation

Fed rats were subjected to 48 h starvation either immediately after partial hepatectomy or sham operation (laparotomy) or at 48 h after partial hepatectomy or sham operation. Rats were sampled at 2 h after intubation with water. Statistically significant effects of partial hepatectomy compared with the sham operation are indicated: * $P < 0.001$; ** $P < 0.001$.

Surgical manipulation	Time of operation (days before onset of starvation)		<i>n</i>	Liver wt. (g/100 g body wt.)	Non-esterified fatty acids (mM)	Liver ketone-body concn. ($\mu\text{mol/g}$ wet wt.)	Blood ketone-body concn. (mM)
None (unoperated controls)	—	Initial	6	3.59 ± 0.07	0.19 ± 0.01	0.54 ± 0.03	0.09 ± 0.02
		Final	6	2.67 ± 0.05	0.44 ± 0.04	1.55 ± 0.08	1.54 ± 0.08
Sham operation	0	Initial	6	3.59 ± 0.07	0.19 ± 0.01	0.54 ± 0.03	0.09 ± 0.02
		Final	4	2.59 ± 0.15	0.74 ± 0.12	1.43 ± 0.08	1.56 ± 0.06
Sham operation	2	Initial	5	3.71 ± 0.20	0.15 ± 0.01	0.53 ± 0.03	0.11 ± 0.03
		Final	6	3.04 ± 0.10	0.38 ± 0.03	1.73 ± 0.05	1.64 ± 0.11
Partial hepatectomy	0	Initial	6	$1.38 \pm 0.08^{**}$	0.19 ± 0.01	0.54 ± 0.03	0.09 ± 0.02
		Final	6	2.34 ± 0.11	0.79 ± 0.12	$0.78 \pm 0.05^{**}$	$0.88 \pm 0.09^{**}$
Partial hepatectomy	2	Initial	5	2.48 ± 0.12	$0.55 \pm 0.06^{**}$	0.41 ± 0.02	0.11 ± 0.03
		Final	6	2.11 ± 0.19	0.42 ± 0.04	$1.22 \pm 0.08^*$	$1.10 \pm 0.15^*$

in rats not subjected to surgical stress the rate of ketone-body clearance correlates with the blood concentration [10], in view of the increased metabolic demands of injury and the fact that 75–90% of energy requirements are met by lipid metabolism (see [14]), the possibility existed that in surgically stressed rats, as in tumour-bearing rats [15], ketone-body utilization was increased. In the present experiments there was no evidence that uncomplicated surgery (laparotomy) influenced ketone-body clearance under conditions where marked effects to decrease ketonaemia were observed (Table 3 and Fig. 5). The lowered ketone-body concentrations found immediately after surgical stress therefore result from decreased ketogenesis.

Although the present experiments do not exclude the possibility that the acute response to trauma results in a redistribution of blood flow such that the supply of ketogenic precursor to the liver is decreased, it is tempting to speculate that decreased ketogenesis is related to an increased hepatic energy requirement, possibly linked to increased rates of gluconeogenesis and ureogenesis (see [14]), with a concomitant increase in the complete oxidation of acetyl-CoA to CO₂. The experiments reported here, utilizing medium-chain triacylglycerol as ketogenic substrate, provide strong support for the importance of such intramitochondrial loci for regulation of ketogenesis.

The regenerating liver after partial hepatectomy has been mainly used as a model for investigating the mechanism of cell proliferation in normal as opposed to cancerous tissue. In animals bearing rapidly growing tumours, peripheral ketone-body utilization is increased even if, on the basis of arterio-venous differences, the tumour does not itself use ketone bodies as substrates [15]. The present results indicate that, despite rapid liver growth, peripheral ketone-body utilization is not increased. The distinction between tumour-bearing and

partially hepatectomized rats may reside in the prevailing level of ketonaemia, marked increases in blood ketone-body concentrations being observed in the former group [15,16]. Alternatively, increased ketone body utilization may be a specific consequence of cancerous growth.

Since ketone-body clearance and its dependence on the level of ketonaemia are unaffected by partial hepatectomy, it can be concluded that ketogenesis is decreased. As both lipolysis and blood flow per unit weight of liver tissue are increased during the early stages of liver regeneration (see [17] for references), intrahepatic control of ketogenesis is indicated. We have previously speculated [3,6] that there may be increased diversion of acetyl-CoA into the tricarboxylic acid cycle during liver regeneration: the present experiments support this idea. After partial hepatectomy, the decreased liver mass not only must increase rates of gluconeogenesis to meet peripheral glucose requirements, but also must provide ATP to fuel cell division and liver growth. On the basis of the results shown in Table 3, it seems likely that the major energy-utilizing process within the remnant liver is cell growth and division, and others have demonstrated that fatty acid oxidation is essential to DNA synthesis and mitosis [18,19]. It is noteworthy that the administration of medium-chain triacylglycerol to partially hepatectomized rats caused a significant (although modest) rise in blood ketone-body concentrations. This finding stresses the possible importance of increased rates of lipogenesis and/or esterification in restricting ketogenesis from endogenous non-esterified fatty acids after partial hepatectomy.

In summary, our results provide evidence for decreased ketogenesis immediately after surgical stress and for up to 2 days after partial hepatectomy. The mechanism by which this is achieved is unknown, but may be related to increased tricarboxylic acid-cycle flux in response to an increased energy demand.

This work was supported by grants from The Nuffield Foundation and the U.K. Medical Research Council. We thank Miss Angela Whibley for expert secretarial assistance.

REFERENCES

1. Sugden, M. C. & Williamson, D. H. (1982) in *Metabolic Compartmentation* (Sies, H., ed.), pp. 287–315, Academic Press, New York and London
2. Tutwiler, G. F. & Delleveigne, P. (1979) *J. Biol. Chem.* **254**, 2935–2941
3. Schofield, P. S., McLees, D. J., Myles, D. D. & Sugden, M. C. (1985) *Biochem. J.* **231**, 225–228
4. Gove, C. D. & Hems, D. A. (1978) *Biochem. J.* **170**, 1–8
5. Mangiapane, E. H., Lloyd-Davies, K. A. & Brindley, D. N. (1973) *Biochem. J.* **134**, 103–112
6. Schofield, P. S., French, T. J., Goode, A. W. & Sugden, M. C. (1985) *FEBS Lett.* **184**, 214–220
7. Smith, R., Fuller, D. J., Wedge, J. H., Williamson, D. H. & Alberti, K. G. M. M. (1975) *Lancet* **i**, 1–3
8. Sugden, M. C., Watts, D. I. & Marshall, C. E. (1982) *Biochem. J.* **204**, 749–756
9. Bremer, J. (1983) *Physiol. Rev.* **63**, 1420–1480
10. Reed, W. D., Baab, P. J., Hawkins, R. G. & Ozand, P. T. (1984) *Biochem. J.* **219**, 15–24
11. Blackshear, P. J., Holloway, P. A. H. & Alberti, K. G. M. M. (1974) *Biochem. J.* **142**, 279–286
12. Robinson, A. M. & Williamson, D. H. (1980) *Physiol. Rev.* **60**, 143–187
13. Isselbacher, J. J. (1968) in *Medium Chain Triglycerides* (Senior, J. R., ed.), pp. 21–34, University of Pennsylvania Press, Philadelphia
14. Elliot, M. & Alberti, K. G. M. M. (1983) in *New Aspects of Clinical Nutrition* (Kleinberger, G. & Deutsch, E., eds.), pp. 247–270, Karger, Basel
15. Rofe, A. M., Bais, R. & Conyers, R. A. J. (1986) *Biochem. J.* **233**, 485–491
16. Magee, B. A., Potezny, N., Rofe, A. M. & Conyers, R. A. J. (1979) *Aust. J. Exp. Biol. Med. Sci.* **57**, 529–537
17. Olivecrona, T. & Fex, G. (1970) *Biochim. Biophys. Acta* **202**, 259–269
18. Nakatani, T., Ozawa, K., Asano, M., Ukikusa, M., Kamiyana, Y. & Tobe, T. (1981) *J. Lab. Clin. Med.* **97**, 887–898
19. Nakatani, T., Yasuda, K., Ozawa, K., Kawashima, S. & Tobe, T. (1982) *Clin. Sci.* **62**, 295–297

Received 27 June 1986/14 August 1986; accepted 24 September 1986