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Carnitine Contents in Remnant Liver, Kidney, and Skeletal Muscle after Partial Hepatectomy in Rats: Randomized Trial

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Abstract. Carnitine, an important carrier of free fatty acid that is transported into mitochondria for beta-oxidation, was thought to be one of the key factors in the regulation of liver regeneration. If the carnitine content is insufficient in the hepatocyte, it might impair the energy substrate's transport and the energy charge required for cell regeneration. The purpose of this study is to evaluate the changes of carnitine content in remnant liver, kidney, and skeletal muscle simultaneously after partial hepatectomy in rats. Partial hepatectomy with resection of the median and left lateral lobes was performed on male Wistar rats. Rats with a sham operation comprised a control group. This study was an experimental randomized trial. Ten rats from each group were sacrificed before the operation and at 6, 24, 48, and 72 hours after the operation. The carnitine content, as total and free forms, in remnant liver, kidney, and skeletal muscle were quantified by high-performance liquid chromatography. The carnitine contents in the remnant liver increased significantly at 6, 24, and 48 hours after partial hepatectomy ($p < 0.01$). The increase of total carnitine content was more obvious than that of the free form. In contrast, the decreasing concentrations of total carnitine and free carnitine in the kidney were significant ($p < 0.01$). In skeletal muscle the total carnitine content decreased to a small extent, and it was observed only at 6 hours after partial hepatectomy ($p < 0.05$). It is suggested that remnant liver promoted the generation of carnitine, whereas kidney and skeletal muscle released their stored carnitine at an early stage after partial hepatectomy. As a result, the influx of the carnitine into hepatocytes increased at the regenerative stage. The carnitine content of remnant liver is sufficient during the early posthepatectomy stage.

Liver regeneration is one of the most rapid forms of tissue growth known in mammals. Many factors such as hormones, growth factors, nutritional components, and pharmacologic agents were proved to affect liver regeneration directly or indirectly [1–3]. Glucose and fat are important energy substrates during the regeneration period after partial hepatectomy [4, 5]. It was proved earlier that the change in energy substrate from glucose to free fatty acid (FFA) took place only during the early posthepatectomy stage [6]. The reason the FFA utilization rate decreased after the early stage is still unclear.

Carnitine, an important carrier of FFA that is transported into mitochondria for beta-oxidation, is believed to play one of the key roles in this regulation. Blaha et al. studied the specific changes in DNA activity and the mitotic activity in carnitine parenterally infused rats [7]. They suggested that L-carnitine has a stimulative and dose-dependent effect on liver regeneration. In addition, acceleration of the onset of liver regeneration by carnitine administration in partially hepatectomized rats was also reported [8]. In contrast, Schofield et al. examined the free carnitine/esterified carnitine ratio in the remnant liver. They found no consequence after the decrease in total carnitine in the remnant liver after partial hepatectomy [9]. French et al. studied tissue carnitine contents in liver and concluded that the capacity of the remnant liver for carnitine biosynthesis is sufficient to maintain the tissue carnitine content, so there is no need to supply dietary carnitine [10]. The effect of carnitine on liver regeneration is still controversial.

In humans carnitine was proved to be synthesized in liver and kidney, stored in skeletal muscle, and excreted mainly in urine [11]. Carnitine homeostasis should be changed during the early posthepatectomy stage. In rats, liver is the sole site of carnitine biosynthesis [10]. Partial hepatectomy in the rat is one way to investigate whether carnitine biosynthesis in the remnant liver can support the needs of liver regeneration and maintain extrahepatic tissue carnitine concentrations. Our previous study has shown that the serum L-carnitine concentration increased significantly at an early stage after partial hepatectomy in rats [12]. Changes in carnitine synthesis, storage, and excretion after partial hepatectomy are still unclear. This study measured the changes in carnitine concentrations in remnant liver, kidney, and skeletal muscle during the early posthepatectomy stage and determined the role of carnitine in the utilization of FFA during this stage.

Materials and Methods

Experimental Protocol

Male Wistar rats purchased from Charles River (Osaka, Japan) were used as subjects. All rats were 8 weeks old and weighed around 200 g; they were randomly assigned to two groups: group I (50 rats), partial hepatectomy followed by usual oral intake (H); group II (50 rats), sham operation followed by the same oral intake (S). All rats were fasted 4 hours before the surgical procedure and 2 hours afterward. They were kept in suspended stainless steel cages (Hsin-Te #MIT, Taipei, Taiwan, ROC) and fed with Purina Rodent Laboratory Chow 5001 diet (a carnitine-

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free diet; the contents include protein 23.4%, amino acids 12.3%, fiber 30.0%, fat 4.5%, nitrogen-free extract 29.8%, and vitamins, with an energy supply of 3.30 kcal/g) in free oral intake.

Surgical Procedure

A midline laparotomy was performed under ether anesthesia. Partial hepatectomy was then carried out by aseptic extirpation of the median and left lateral lobes according to the procedure of Higgins and Anderson [13]. Laparotomy was performed only in the sham-operated rats. All procedures were performed strictly between 8 and 11 a.m. to reduce the influence of diurnal variation in plasma hormone levels. Ten rats from each group were sacrificed before and at 6, 24, 48, and 72 hours after the operation. Blood samples and tissues from the remnant liver, left kidney, and skeletal muscle from the left thigh were obtained; and all measurements were carried out. All operations were performed by the same surgeon to reduce surgical technical variation.

Measurements

High-performance liquid chromatography (HPLC) was used to quantify the free carnitine contents in remnant liver, kidney, and skeletal muscle, as reported by Arakawa et al. [14]. Briefly, a weighed tissue (around 0.3 g) was immediately cut into small pieces and homogenized in eight volumes of 6% cold $HClO_4$ with a Potter-Elvehjem homogenizer. The homogenates obtained were centrifuged at 5,000 $\times$ *g* for 10 minutes. The pellet was washed with 6% $HClO_4$ and centrifuged again. The supernatant and the tissue washings were combined and kept at -80°C before the analysis.

For hydrolysis of acylcarnitine for total carnitine analysis, 1 ml of tissue or plasma supernatant was added with 1 ml of 1 N KOH and incubated at 25°C for 30 minutes. The solution was neutralized with 6% $HClO_4$ and assayed for free carnitine. Short-chain acylcarnitine content was determined by subtracting the value of free carnitine from that of acid-soluble carnitine.

For free carnitine analysis, tissue supernatants were neutralized with KOH and allowed to stand for 30 minutes on ice. After centrifugation the supernatant was filtered through a Millipore HV filter (0.45 μm; Nihon Millipore, Kogyo, K.K., Japan) and used for the enzyme reaction assay. The reaction mixture, in a final volume of 1 ml, contained 0.5 μmol EDTA, 10 μmol phosphate buffer (pH 7.5), 40 nmol acetyl coenzyme A (CoA), and the tissue supernatant (0.1–5.0 nmol carnitine). The reaction was initiated by the addition of 1 U carnitine acetyltransferase (CAT). After incubation at 25°C for 30 minutes the mixture was adjusted to pH 2 with H_3PO_4 and then analyzed by HPLC.

A Hitachi 638 liquid chromatograph equipped with a syringe loading sample injector (model 7125) was used. The eluate was monitored by an ultraviolet detector of 254 nm wavelength. A stainless steel column (25 cm $\times$ 4.6 mm i.d.) was packed with Ultrasphere Octyl C8 (5 μm) (Beckman, Fullerton, CA, USA). A solvent mixture of 190 mM KH_2PO_4 and methanol (87:13, v/v) at a flow rate of 0.7 ml/min was used for the mobile phase. A 10-μl aliquot of each sample was injected.

Statistical Analysis

All experimental data are expressed as the mean $\pm$ SD. The significance of difference among all groups was analyzed using one-way ANOVA.

Results

The changes in carnitine contents in the remnant liver after partial hepatectomy are shown in Figure 1. The total tissue carnitine concentration increased significantly at the early stage (396 $\pm$ 36 nmol/g preoperatively to 548 $\pm$ 49 nmol/g 6 hours after partial hepatectomy). The concentration continues to increase until 24 hours (649 $\pm$ 61 nmol/g) and 48 hours (775 $\pm$ 85 nmol/g) and then decreases to the preoperative level at 72 hours (477 $\pm$ 48 nmol/g). The free carnitine concentration in the remnant liver showed a similar trend. It increased significantly from 24 to 48 hours after partial hepatectomy compared to the preoperative concentration and that in sham-operated rats. The free/total carnitine ratio decreased from 42.4% preoperatively to 33.2%, 34.8%, and 36.9% at 6, 24, and 48 hours after partial hepatectomy. It then returned to 41.5% at 72 hours after partial hepatectomy. The ratios ranged between 40.2% and 51.2% in sham-operated rats during this study.

The change of carnitine content in kidney is shown in Figure 2. Different from the changes in remnant liver, the total and free carnitine concentrations decreased significantly 6 hours after partial hepatectomy (235 $\pm$ 23/100 $\pm$ 12 nmol/g preoperatively to 185 $\pm$ 23/78 $\pm$ 11 nmol/g). The decrease persisted and was more marked at 24 hours (82 $\pm$ 14/46 $\pm$ 8 nmol/g) and 48 hours (101 $\pm$ 17/48 $\pm$ 7 nmol/g) postoperatively. It then returned to near the preoperative level 72 hours after partial hepatectomy (199 $\pm$ 20/98 $\pm$ 12 nmol/g). The free/total carnitine ratio showed no remarkable changes when compared with that of the sham-operated rats.

The changes of carnitine content in skeletal muscle from the left upper thigh showed a less marked pattern (Fig. 3). The total carnitine concentration decreased from 502 $\pm$ 62 nmol/g preoperatively to 388 $\pm$ 50 nmol/g 6 hours after partial hepatectomy ($p < 0.05$). The free carnitine concentration was low (122 $\pm$ 14 nmol/g), but it showed no significant difference from the preoperative data (146 $\pm$ 18 nmol/g) or the sham-operated rats' data (134 $\pm$ 16 nmol/g). The free/total carnitine ratio increased slightly (from 27.9% to 31.4%) at this time, but it returned to the preoperative level at 24 hours and persisted until 72 hours after partial hepatectomy. There was no significant change in carnitine content in the liver, kidney, or skeletal muscle in sham-operated rats.

Discussion

Liver regeneration was proved to be remarkable when it was quantified by remnant liver weight, mitotic index, and DNA synthesis rate after partial hepatectomy in rats [1, 13, 15]. The DNA synthesis rate increased abruptly to a peak 24 hours after operation. The mitotic index reached a maximum level at 48 hours, and the remaining lobes had doubled in size at the same time and had attained around 90% of the normal liver size 72 hours after partial hepatectomy. Whether glucose or fatty acid is the major energy substrate during the early phase after partial

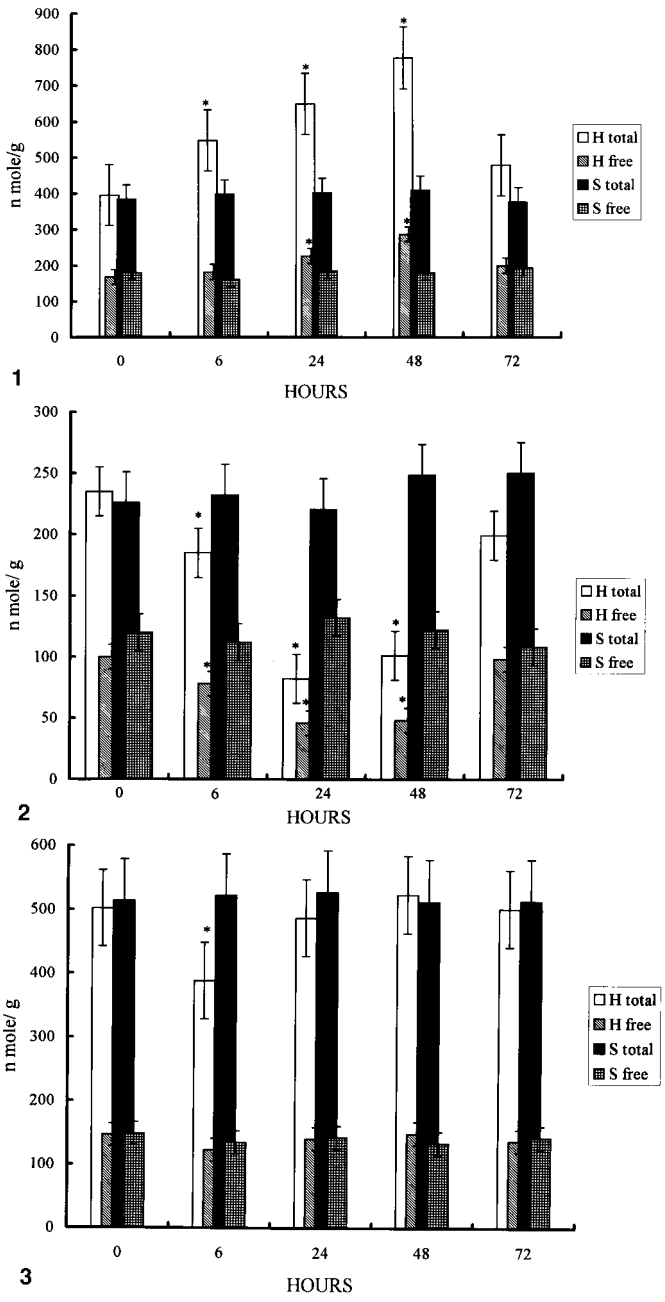

Fig. 1. Changes of total and free carnitine contents in remnant liver at 6, 24, 48, and 72 hours after surgery in hepatectomized rats (H) and sham-operated rats (S) (mean ± SD). *H vs. S, $p < 0.01$.

Fig. 2. Changes of total and free carnitine contents in kidney at 6, 24, 48, and 72 hours after surgery in hepatectomized rats (H) and sham-operated rats (S) (mean ± SD). *H vs. S, $p < 0.01$.

Fig. 3. Changes of total and free carnitine contents in skeletal muscle at 6, 24, 48, and 72 hours after surgery in hepatectomized rats (H) and sham-operated rats (S) (mean ± SD). *H vs. S, $p < 0.01$).

hepatectomy is still controversial. Many studies have suggested that the energy source in remnant liver shifts to predominant utilization of fatty acid when the energy charge decreases in the hepatocytes. It then begins to utilize glucose again when glucose is available and the energy charge level is restored [4, 16, 17]. The mechanism for this shifting of the energy substrate remains unclear.

It was proved in our previous work that FFA is considered an important energy source for the initial posthepatectomy regenerative phase by evidence derived from serum FFA levels, total ketone bodies (TKB), and the ketone body ratio (KBR: acetoacetate/β-hydroxybutyrate) [12]. There was a sharp increase in serum FFA (265%) 6 hours after operation, after which it decreased gradually and returned to the preoperative level 72 hours after partial hepatectomy. TKB also increased to 187% of preoperative levels 6 hours postoperatively and returned gradually. The KBR decreased to 0.595 at 6 hours and returned to 0.877 at 72 hours. According to these results, the utilization of FFA occurred only during the early posthepatectomy stage and decreased later. The regenerative condition of remnant liver was even worse in the rats fed with excess fat than those fed with excess glucose and the control group rats [6].

Mitochondrial respiration, especially the respiratory index and adenosine triphosphate (ATP) synthesis, increased remarkably in the regenerating hepatocytes [18]. However, the liver regeneration rate decreased when octanoylcarnitine, a potent inhibitor of fatty acid oxidation, was infused intraportally after 70% hepatectomy in rabbits [19]. Carnitine, the carrier of fatty acid into mitochondria for beta-oxidation, was thought to play an important role during the early regenerating phase after partial hepatectomy. Carnitine has two main functions: transporting long-chain fatty acids into the mitochondrial matrix for beta-oxidation and modulating the rise in intramitochondrial acyl-CoA/CoA ratio [11]. It is believed that the main consequence of carnitine deficiency is impairment of energy metabolism used for hepatocyte regeneration.

Caruso et al. studied the relation between plasma carnitine levels and liver regeneration and suggested that the plasma carnitine level be considered a liver regeneration index [20]. French et al. proved later that the plasma carnitine concentration was affected in surgically stressed rats as well as in partially hepatectomized rats [21]. Rebouche and Engel estimated that 95% of the carnitine pool is in skeletal muscle and heart, 1% in extracellular fluid, and 4% in other tissues, such as liver and kidney [22]. When FFA is utilized during the early posthepatectomy stage, the carnitine contents in remnant liver, kidney, and skeletal muscle might be different.

This study showed that the remnant liver carnitine content, both free and esterified forms, increased significantly 6 hours after partial hepatectomy. This phenomenon is consistent to the result of our previous study that the serum L-carnitine level was elevated significantly at the early stage after partial hepatectomy [12]. The serum L-carnitine level increased markedly at 6 hours, persisted until 48 hours, and increased further at 72 hours after partial hepatectomy. It seems that enough carnitine was stored in the remnant hepatocytes to bring sufficient FFAs into mitochondria for beta-oxidation and to obtain more energy for the regenerative activities of the hepatocytes. The decreased free/total carnitine ratio in the remnant liver means that more of the increased biosynthesized carnitine was utilized and became the esterified form during the metabolic process of regeneration. Results also showed that the carnitine content decreased markedly in kidney at the same time, although the decrease in carnitine in skeletal

muscle was mild and lasted only a short time (6 hours after operation).

It is suggested that kidney and skeletal muscle released their stored carnitine into serum at this stage, and as a result the influx of carnitine into hepatocytes was increased. The efflux of carnitine from kidney and skeletal muscle is due to the changes in the circulating fatty acid levels or the hormonal signals involved during the liver-regenerating period. The mild change in carnitine concentrations in skeletal muscle was due to the fact that skeletal muscle makes up a large percentage of the body weight and has a large amount of carnitine; therefore the change in the muscle carnitine concentration was not obvious after partial hepatectomy.

A sufficient carnitine concentration in serum and hepatocytes ensured a sufficient amount of fatty acid for beta-oxidation in mitochondria. Unfortunately, the utilization of FFA decreased 24 hours after partial hepatectomy. The process then reversed, and the tissue carnitine returned to the preoperative level in remnant liver, kidney, and skeletal muscle. The carnitine concentration in the remnant liver has a full response to the stimulation of partial hepatectomy. The homeostasis reaction has suggested the need for carnitine in the regeneration of hepatocytes at an early posthepatectomy stage. It indicated that the carnitine content is sufficient at this stage. Carnitine is not the main factor that decreases utilization of fatty acid in the regenerating liver in hepatectomized rats. Additional studies on the cytoplasmic environment, including intracellular fat metabolism, hormone changes, protein by-products, and variations of pH value, are recommended.

Résumé

On pense que la carnitine, un transporteur essentiel des acides gras libres vers la béta-oxydation dans les mitochondries, est un facteur important dans la régulation de la régénération du foie. Si le contenu en carnitine est insuffisant dans l'hépatocyte, le transport d'énergie et la charge en énergie pour la régénération cellulaire pourraient se trouver déficients. L'objectif de cette étude a été d'évaluer, par randomisation, les changements du contenu de carnitine dans le foie restant, le rein et le muscle squelettique après hépatectomie partielle chez le rat. On a réalisé des hépatectomies partielles comprenant l'ablation des lobes médians et latéraux chez des rats Wistar mâles. Dans le groupe contrôle les rats ont eu une opération factice («sham»). Dans chaque groupe, on a sacrifié 10 rats avant l'opération et 6, 24, 48, et 72 heures après l'intervention. On a mesuré le contenu en carnitine, sous forme totale et libre, dans le foie restant, le rein et le muscle squelettique, quantifiés par la chromatographie liquides à haute performance. Le contenu en carnitine du foie restant était augmenté de façon significative 6, 24 et 48 heures après l'hépatectomie partielle ($p < 0.01$). L'augmentation du contenu en carnitine totale étalt plus prononcée que celle du contenu en carnitine libre. En revanche, dans le rein, on a observé une chute significative du contenu en carnitine totale et libre ($p < 0.01$). Dans le muscle squelettique, le contenu en carnitine totale diminuait modérément et ce, seulement 6h après l'hépatectomie partielle ($p < 0.05$). On suggère que le foie restant stimulait la génération de carnitine alors que le rein et le muscle squelettique larguaient leur carnitine à des stades plus précoces après l'hépatectomie partielle. Il en résultait l'augmentation de l'entrée de carnitine dans l'hépatocyte au stade de la régénération. Le contenu en carnitine du foie restant est suffisant pendant la période précoce post-hépatectomie.

Resumen

Se ha considerado que la carnitina, un importante transportador de ácidos grasos libres que ingresan a la mitocondria para la beta oxidación, es uno de los factores clave en la regulación de la generación hepática. La insuficiencia en el contenido de carnitina en el hepatocito puede alterar el transporte del sustrato energético y la carga energética necesarios para la regeneración celular. El propósito del presente estudio es evaluar los cambios en el contenido de carnitina en el hígado remanente, y simultáneamente en el riñón y el músculo esquelético, luego de hepatectomía parcial en ratas. Se practicó una hepatectomía parcial con resección de los lóbulos mediano y lateral en ratas Wistar machos, con un grupo control constituido por ratas con operación fantasma (Shaun), en un estudio experimental y randomizado. Diez ratas de cada grupo fueron sacrificadas antes de la operación y a los 6.24, 48 y 72 horas luego de la operación. Se hizo la cuantificación del contenido de carnitina, tanto en su forma total como en su forma parcial, en el hígado remanente, el riñón y el músculo esquelético, mediante cromatografía líquida de alto rendimiento. El contenido de carnitina aumentó significativamente en el hígado remanente a las 6,24 y 48 horas luego de la hepatectomía parcial ($p < 0.01$). El incremento de la carnitina total apareció más evidente que el de la carnitina libre. Por el contrario, la tasa descendiente de contenido de carnitina total, así como la de contenido de carnitina libre en el riñón, son significativas ($p < 0.01$). En el músculo esquelético, el contenido total de carnitina descendió en forma leve y apenas pudo ser observado a las 6 horas luego de la hepatectomía parcial ($p < 0.05$). Se sugiere que el hígado remanente promueve la generación de carnitina, en tanto que el riñón y el músculo esquelético liberan sus reservas de carnitina en las primeras etapas después de la hepatectomía parcial. El resultado es que el influjo de carnitina al hepatocito se aumenta en la etapa regenerativa. El contenido de carnitina en el hígado remanente es suficiente durante la etapa muy temprana posthepatectomía.

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Invited Commentary

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Enhancement of liver mitochondrial oxidative and phosphorylative activities may play a key role in restoration after the energy crisis resulting from the overwhelming metabolic load on the remnant liver after major hepatectomy. Isolated mitochondria from the remnant liver during the early phase after major hepatectomy showed enhancement of oxidative and phosphorylative activities when the energy charge decreased. One hallmark of the regeneration process is enhanced DNA synthesis, an energy-dependent reaction.

Infusion of hyperosmolar glucose solution has been recommended for this period, although utilization of glucose as a substrate for energy generation is greatly impeded during the early stage after major hepatectomy [1]. Increases in serum fatty acids during the early posthepatectomy phase are considered prerequisite for predominant utilization of fatty acids in the remnant liver. From the clinical point of view, whether glucose or fatty acid is the major energy substrate during the early phase is crucially important but still controversial.

Fatty acids are the major energy substrate during the early phase. It was previously reported that the remnant liver metabolism switches to predominant utilization of fatty acids as an energy substrate, as shown by the experiment where portal infusion of (+)−octanoylcarnitine, a potent inhibitor of fatty acid oxidation, affects liver mitochondrial energy metabolism early after major hepatectomy. It then reverts to utilization of glucose to restore the energy charge [2]. Mitochondria isolated from the remnant liver showed enhancement of ketogenesis concomitant with enhancement of mitochondrial phosphorylative activities, suggesting enhancement of fatty acid oxidation [3].

Hyperosmolar glucose solution or insulin administration during the early phase should be restricted because each inhibits mobilization of free fatty acid (FFA) from peripheral adipose tissue.

The present study shows changes in carnitine content (an essential factor for transportation of long-chain fatty acid into mitochondria) in major carnitine pools such as liver, kidney, and muscle. They previously reported an increase in serum carnitine during the early phase after major hepatectomy. Although the decrease in muscle carnitine content is less prominent because of its larger carnitine pooling capacity, carnitine mobilization to liver from kidney and muscle during the early phase is clearly shown after major hepatectomy, when fatty acid oxidation is considered to be enhanced.

Although the mechanism has yet to be clarified, carnitine mobilization to the remnant liver may play a key role in enhancement of FFA oxidation in mitochondria, leading to the restoration of energy status. We expect further investigations to seek the efficient way to produce energy after hepatectomy.

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