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Effects of L-Carnitine on Propofol-Induced Inhibition of Free Fatty Acid Metabolism in Fasted Rats and *in Vitro*

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Abstract

Background: Propofol inhibits fatty acid oxidation and induces mitochondrial deficiency, a possible mechanism involved in propofol infusion syndrome. This study investigated how propofol influences fatty acid, glucose, and amino acid metabolism, as well as whether L-carnitine may improve suppression of free fatty acid metabolism. **Methods:** Male Sprague-Dawley rats, fasted for 16 hours, were allocated to the following two groups: (Group P; continuous intravenous administration of 10 mg/kg/h propofol; n = 8) and (Group P + C; intravenous administration of 50 mg/kg and then 50 mg/kg/h L-carnitine continuously; n = 8). Concentrations of glucose, free fatty acid (FFA), amino acids, insulin, and β-hydroxybutyric acid were measured at the start and then one, two, and three hours after propofol administration. Intrahepatic triglyceride levels were measured at the end of experiments. *In vitro* experiments comprised measurement of oxygen consumption in human hepatocytes (Hepg2) and investigating dependency on palmitic acid, glucose, and glutamine as fuel during propofol administration, with or without L-carnitine. **Results:** FFA increased in Group P and gradually decreased in Group P + C. There were significant differences between the two groups (Group P; 331.2 ± 64.5 μM vs. Group P + C; 199 ± 73.6 μM). Glucose decreased in both groups (Group P; 53.8 ±16.6 mg/dL vs. Group P + C; 88 ± 11.3 mg/dL). Amino acid concentrations were higher in Group P + C after experiments; alanine and glutamine increased significantly. β-hydroxybutyric acid increased significantly in Group P + C, and intrahepatic triglyceride decreased in Group P + C. Dependency on fatty acid metabolism significantly decreased with propofol only; addition of L-carnitine prevented these effects. **Conclusions:** Propofol impaired mitochondrial fatty acid metabolism, which was compensated

mainly by a switch to glucose metabolism and partially by amino acid metabolism. Addition of L-carnitine may improve this imbalance of energy metabolism.

Keywords

Propofol, L-Carnitine, Free Fatty Acids, Mitochondria, Oxygen Consumption

1. Introduction

Propofol is widely used for intravenous induction and/or maintenance of general anesthesia as well as sedation of patients in intensive care units. Propofol use has increased due to the agent's rapid onset and offset, and the superior quality of sedation it produces. However, propofol has several side effects such as hypotension, bradycardia, respiratory depression and suppression of cardiac contractility. One of the most serious complications, however, is propofol infusion syndrome (PRIS).

PRIS may present clinically with arrhythmias, hyperlipidemia, fatty liver, metabolic acidosis, and rhabdomyolysis, and may be fatal [1] [2] [3]. The pathological mechanism of PRIS is still unclear, but two chief theories exist. One possible mechanism is that propofol interacts with coenzyme Q, impeding the flow of electrons in the mitochondrial respiratory chain [4]. Another proposed mechanism is that propofol inhibits fatty acid oxidation and induces mitochondrial deficiency [5] [6]. Propofol is known to inhibit the effects of carnitine palmityl transferase 1 (CPT 1), a protein which transports long-chain fatty acids into the mitochondria [5]. Animal experiments have shown that propofol impairs the mitochondrial electron transport chain in isolated heart preparations [7]. Another animal study demonstrated inhibition of fatty acid transport into mitochondria at the level of carnitine-acyl transferase 1 [8]. A previous study reported that plasma concentrations of acylcarnitine derivatives increased in children with PRIS, suggesting propofol induced defective fatty acid oxidation [9].

Glucose and fatty acids are the chief substrates used by the human body to generate energy. Preference for one or the other relies on age, hormonal influences, and the type of organ or tissue. Fatty acid metabolism is an important energy source in several situations, such as hunger, starvation, infection, and diabetic ketoacidosis. In situations where a high dependency on fatty acid metabolism exists, propofol-induced impairment of fatty acid oxidation may lead to critical and serious conditions such as PRIS.

L-carnitine is a small, highly polar, water-soluble, quaternary amine, present in the human body from both endogenous synthesis and exogenous intake. The chief function of L-carnitine is to support transportation of long-chain fatty acids across the inner mitochondrial membrane. Sufficient supplementation of

L-carnitine may facilitate the metabolism of free fatty acid (FFA). It is known that carnitine deficiency leads to impairment of both free fatty acid transport and mitochondrial β oxidation [10]. We hypothesized that administration of L-carnitine could prevent propofol-induced inhibition of fatty acid oxidation.

The purpose of the present study was twofold: firstly, to investigate how administration of propofol with or without the addition of L-carnitine influences fatty acid, glucose, and amino acid substrate levels *in vivo*, and secondly, how propofol with or without L-carnitine affects FFA metabolism in isolated human hepatocytes. We also considered whether L-carnitine could improve the propofol-induced suppression of FFA metabolism, as this may decrease the incidence of PRIS.

2. Materials and Methods

1) *In Vivo* Experiments

All study protocols were approved by the Animal Research Ethics Committee of the Faculty of Medicine at Kagoshima University (Kagoshima, Japan). Male Sprague-Dawley rats (200 - 250 g; Kyudo, Saga, Japan) were used for all experiments. All animals were housed at constant temperature and humidity with 12:12 hour light/dark cycles. Rats were allowed free access to food and water but were fasted for 16 hours before experiments.

Animals were allocated to two groups as follows: a Propofol Group (Group P, n = 8) and a Propofol + L-Carnitine Group (Group P + C, n = 8). Anesthesia was induced with intraperitoneal injection of pentobarbital (40 mg/kg; Abbott Laboratories, North Chicago, IL). After inserting a 14-gauge needle into the trachea, all rats underwent catheterization of both the right external jugular vein and right carotid artery for blood sampling and measurement of blood pressure. In both groups, propofol (AstraZeneca K.K., Osaka, Japan) was continuously infused via the jugular vein at the rate of 10 mg/kg/h. In the P + C Group, L-carnitine (Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan) was given as a 50 mg/kg intravenous bolus, then continuously administered at 50 mg/kg/h. Group P received the same dose of 0.9% saline instead of carnitine.

Blood was collected at four points: at the start of the experiments and then one, two, and three hours after propofol administration, to measure concentrations of FFA, glucose, amino acids, insulin, and β-hydroxybutyric acid. Sampled blood was centrifuged at 3000 rpm for 10 minutes to separate plasma. The animals' livers were removed and quick-frozen at the end of the experiments for measurement of intrahepatic triglycerides. Plasma and frozen liver samples were stored −80˚C until analysis. FFA and β-hydroxybutyric acid were measured using ELISA kits (Cell Biolabs, San Diego, USA and Cayman Chemical, Michigan, USA). Plasma amino acid concentrations were determined with a JLC-500 model amino acid analyzer (JEOL, Tokyo, Japan) after deproteinization with 5% (w/v) sulfosalicylic acid [11]. Triglyceride concentrations were measured using a TG-E test (Wako, Japan).

2) ***In Vitro* Experiments**

Human hepatocytes (Hepg2) were purchased from ATCC (Rockville, USA). Hepg2 cells were grown in Dulbecco's modified Eagle's medium, supplemented with 10% fetal bone serum and 1% penicillin/streptomycin. Cells were seeded in 60 mm dishes and incubated at 37˚C in an atmosphere of 5% CO_2 and grown at 80% confluence before use. Mitochondrial utilization of palmitate, glucose, and glutamine as fuel was studied in Hepg2 cells, in the presence and absence of 100 μM propofol (2.6-diisopopylphenol) or 100 μM L-carnitine, which were purchased from Sigma-Aldrich (St. Louis, MO, USA). This was measured using an XFp Analyzer to perform an XFp Mito Fuel Flex Test according to the manufacturer's instructions (Seahorse Bioscience, Copenhagen, Denmark), as detailed [12]. Briefly, Hepg2 cells were seeded at 2×10^4 cells per well and cultured for 24 hours to near 80% confluence before measurements exposed to the following media using Dulbecco's modified Eagle's medium:

Group A: the same doses of phosphate-buffered saline (n = 6);

Group B: 100 μM Propofol (n = 6);

Group C: 100 μM propofol + 100 μM L-carnitine (n = 6).

Before the assay, cultures were washed three times with XF Assay Dulbecco's modified Eagle's medium (unbuffered; Seahorse Bioscience) containing 1 mM pyruvate, 2 mM glutamine, and 10 mM glucose, and then incubated for one hour in a 37˚C non-CO_2 incubator. The XFp Analyzer determined the oxygen consumption rate (OCR) for each fuel by adding relevant pathway inhibitors (2 MUK5099, 3 μM BPTES, and 4 μM Etomoxir, for the glucose, glutamine, and fatty acid pathways, respectively).

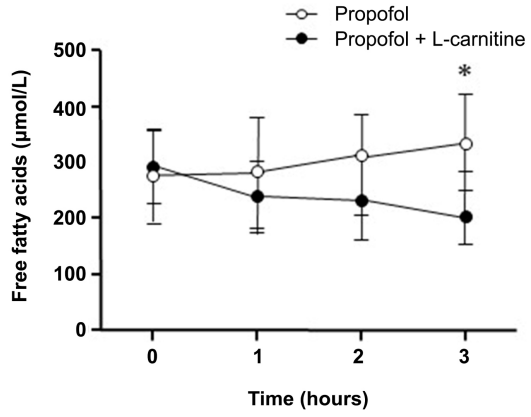
3) **Statistical Analysis**

Data are expressed as the mean ± standard deviation (SD). Values of $p < 0.05$ were considered statistically significant. Plasma concentrations of FFA, glucose, and insulin were analyzed using two-way repeated-measures analysis of variance (ANOVA). The concentrations of β-hydroxybutyric acid and intrahepatic triglyceride were analyzed using unpaired t-test. One-way ANOVA was performed to compare dependency on fatty acid, glucose, and glutamine among the three *in vitro* groups. All statistical analyses were performed using GraphPad Prism 5.0 software (GraphPad Software, Inc., La Jolla, CA, USA).

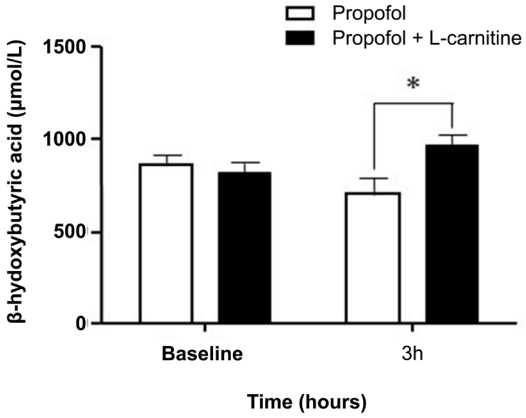
3. Results

1) ***In Vivo* Experiments**

Plasma concentrations of FFA increased in Group P and decreased in Group P + C. This process occurred gradually in both groups. There were significant differences between the two groups (Group P, 331.2 ± 64.5 μM vs. Group P + C, 199 ± 73.6 μM; $p < 0.05$; **Figure 1(a)**). The plasma concentrations of β-hydroxybutyric acid in Group P had not changed from baseline at the three-hour time point, whereas in Group P + C this had increased significantly compared with both baseline and Group P (**Figure 1(b)**). Glucose concentrations



(a)



(b)

Figure 1. Plasma concentrations of FFA and β-hydroxybutyric acid. FFA concentrations were measured prior to and then one, two, and three hours after administration of propofol (10 mg/kg/h) or propofol and L-carnitine (initially 50 mg/kg and then 50 mg/kg/h). FFA concentrations in Group P had increased gradually and there were significant differences between the two groups at three hours. β-hydroxybutyric acid concentrations were measured at three hoursfollowing administration. The concentrations in Group P + C were significantly higher compared to Group P. Data are expressed as the mean ± SD. $^{*}p < 0.05$.

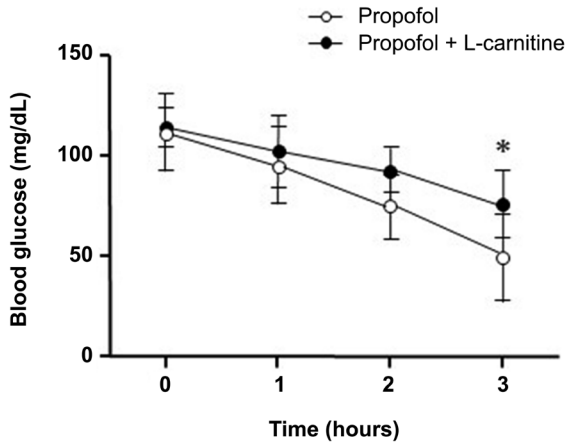
decreased in Group P and P + C (53.8 ± 16.6 mg/dL and 88 ± 11.3 mg/dL, respectively at the three-hour time point; $p < 0.05$). There was a prominent decline in Group P and there were significant differences in glucose concentrations between the two groups. However, there were no significant differences in insulin concentrations during the procedures (Figure 2(a), Figure 2(b)). Higher concentrations of amino acids (alanine, glutamine, valine, leucine, and isoleucine) were found in Group P + C when compared with Group P at the end of the experiments, with significant increases in alanine and glutamine ($p < 0.05$) (Table 1). Moreover, intrahepatic triglyceride levels at the end of experiments in the Group P and P + C were 6.4 ± 1.2 mg/dL and 2.1 ± 0.4 mg/dL, respectively ($p < 0.05$, Figure 3).

2) *In Vitro* Experiments

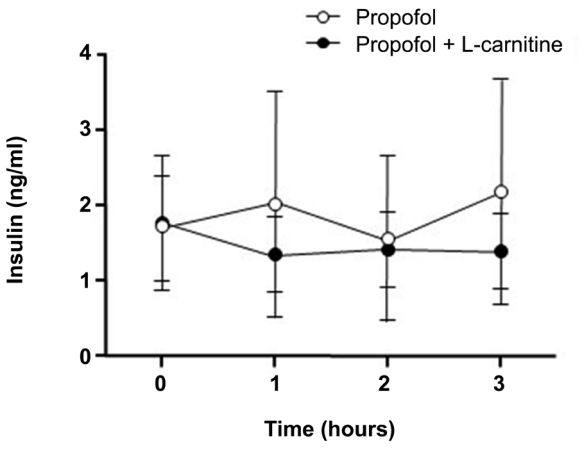
Table 1. Plasma amino acid concentrations.

	Propofol	Propofol + L-carnitine
Valine	158.7 ± 14.9	194.5 ± 10.8
Leucine	126.6 ± 13.9	149.8 ± 12.6
Isoleucine	77.8 ± 10.6	99.8 ± 11.6
Alanine	455.6 ± 34.8	783.6 ± 121.6*
Glutamine	698.1 ± 61.2	896.3 ± 34.8*

Concentrations of BCAA (Valine, Leucine, Isoleucine) in the propofol + L-carnitine group were higher than in the propofol group, but not significantly so. Concentrations of alanine and glutamine in the propofol + L-carnitine group were significantly higher compared to the propofol group. Data are expressed as the mean ± SD. *$p < 0.05$ versus propofol group.



(a)



(b)

Figure 2. Plasma concentrations of blood glucose and insulin. Glucose and insulin concentrations were measured prior to and then one, two, and three hours after commencing administration of propofol (10 mg/kg/h) or propofol and L-carnitine (initially 50 mg/kg and then 50 mg/kg/h). Glucose concentrations in Group P + C were significantly higher three hours after starting administration, compared to Group P. There were no significant differences in insulin concentrations between the two groups for all procedures. Data are expressed as mean ± SD. *$p < 0.05$.

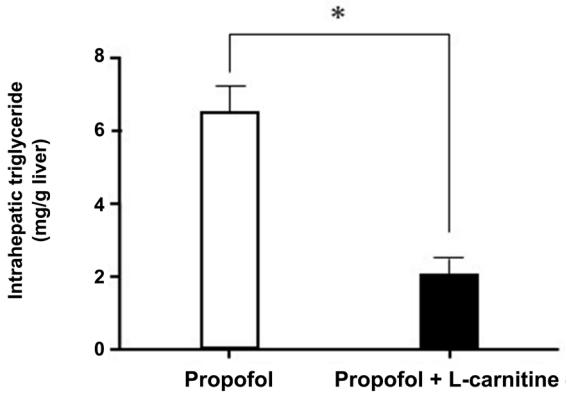


Figure 3. Intrahepatic triglyceride concentrations. The concentration of intrahepatic triglyceride in Group P was high. Co-administration of L-carnitine may preventsignificant accumulation of triglyceride in the liver. Data are expressed as mean ± SD. *$p < 0.05$.

OCR in the mitochondria of Hepg2 cells were measured at baseline before adding each inhibitor and at various time points thereafter. **Figure 4** demonstrates cell dependence on different fuels (fatty acid, glucose, and glutamine) as ΔOCR (pmol/min), which was analyzed using the following formula:

ΔOCR (pmol/min) = baseline OCR – OCR after adding inhibitor

ΔOCR in fatty acid metabolism significantly decreased with addition of propofol, but co-administration of L-carnitine could prevent these effects ($p < 0.05$). On the other hand, addition of propofol increased ΔOCR in both glucose and glutamine metabolism; co-administration of L-carnitine partially prevented this effect.

4. Discussion

It is well known that propofol toxicity leads to impaired mitochondrial fatty acid metabolism. This was borne out with our experimental results. In the present study, we also showed that propofol-induced inhibition of fatty acid metabolism may be chiefly or partially compensated by glucose or amino acid metabolism, respectively. We also demonstrated the beneficial effect of additional L-carnitine.

Fatty acids represent an important fuel source in the fasting state. Triglycerides are disassembled in fatty tissue while free fatty acids are transported in the blood bound to albumin. As such, an insufficient supply of fatty acid may result in serious damage to the mitochondria, tissue, and organs when demand exists. Many experiments had showed that impaired β oxidation of fatty acids may result in hypoglycemia. $NADH_2^+$ and acetyl-coenzyme A (acetyl-CoA) are produced during β oxidation, which is then metabolized with production of $NADH_2^+$ in the tricarboxylic acid cycle. In the present study, propofol inhibited this metabolism and increased plasma concentrations of FFA. In our pilot study, we had recognized that the administration of Intralipid® (Terumo Co., Tokyo Japan), a lipid emulsion used in propofol preparations, was unable to increase FFA concentrations (**Figure 5**). These results suggest that β oxidation of fatty

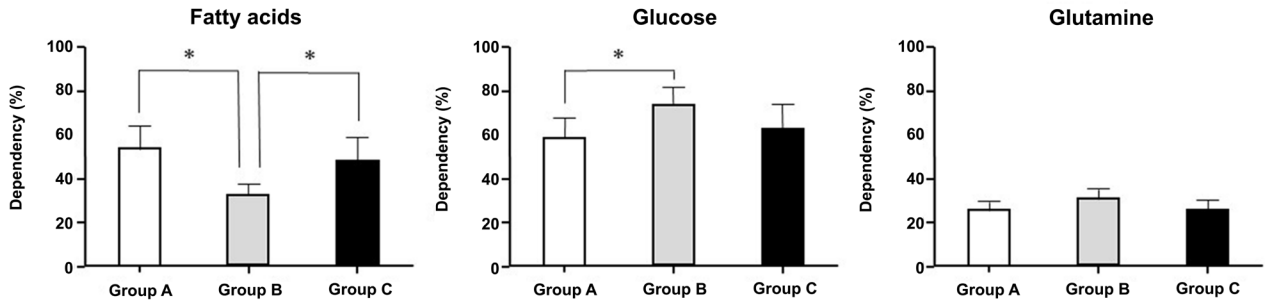


Figure 4. Dependency on fatty acids, glucose, and glutamine as energy fuel. Group A) The same doses of Phosphate Buffered Saline; Group B) 100 μM propofol; Group C) 100 μM propofol + 100 μM L-carnitine. Oxygen consumptions were measured using an XFp analyzer to investigate dependency on fatty acid, glucose, and glutamine as fuel. Mitochondrial fuel usage rates for fatty acid, glucose, and glutamine in Hepg2 cells are shown as percentages with or without 100 μM propofol (2.6-diisopopylphenol) or 100 μM L-carnitine. Dependency on fatty acid in group B decreased significantly compared to Group A, however, this decreased effect was significantly inhibited in Group C. Glucose dependency in Group B increased significantly compared to group A. Data are expressed as the mean ± SD. $^*p < 0.05$.

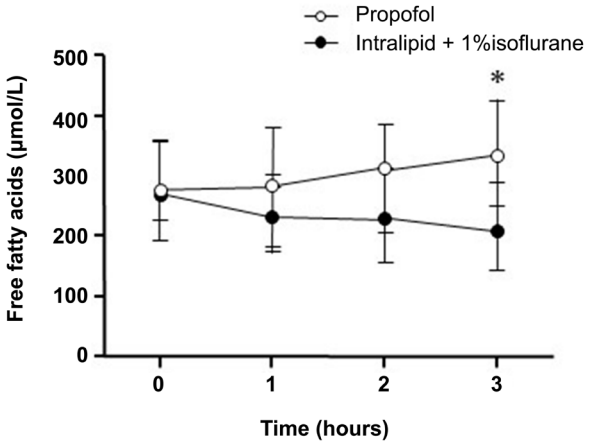


Figure 5. Free fatty acid concentrations in the pilot study. FFA concentrations were measured prior to and then one, two, and three hours after administration of propofol (10 mg/kg/h) or the same dose of Intralipid under 1% isoflurane anesthesia. At three hours, FFA concentrations in the propofol group had increased gradually and there were significant differences between the two groups. In the Intralipid group, there were no significant changes in FFA concentrations during experimental procedures. Data are expressed as the mean ± SD. $^*p < 0.05$.

acids was not induced by propofol. *In vivo* experiments revealed a marked decrease in concentrations of blood glucose as well as the glycogenic amino acids alanine and glutamine. This suggests that propofol administration may inhibit glycogenesis.

As L-carnitine transfers long chain fatty acids from the cytosol into mitochondria for β oxidation, L-carnitine or CPT deficiencies result in inhibition of β oxidation and glycogenesis, with subsequent hypoketonic hypoglycemia [13] [14]. Our *in vivo* experiments suggest that co-administration of L-carnitine may improve FFA metabolism and prevent the incremental increases in FFA concentration induced by propofol. The results also suggest that glycogenesis and hy-

poketonic hypoglycemia were prevented by addition of L-carnitine.

The *in vitro* experiments investigated metabolic dependency on palmitate, glucose, and glutamine for energy production following propofol-induced inhibition of palmitate as an energy-producing substrate. Glucose utilization increased markedly, while glutamine metabolism did so partially when propofol impaired the metabolism of palmitic acid. Co-administration of L-carnitine could improve the utilization of palmitic acid and prevent the compensatory dependence on glucose and glutamine for energy production. These results suggest that L-carnitine prevents propofol-induced inhibition of fatty acid oxidation. It is possible that this inhibition may be one of the mechanisms involved in the development of PRIS.

L-carnitine may also offer additional anti-oxidative protection in several different tissues and organs, such as the brain, heart, liver, and kidneys [15] [16] [17] [18]. Oxidative stress may contribute to impaired mitochondrial function; as such, L-carnitine's anti-oxidative effects may help prevent the incidence of PRIS.

The clinical features of PRIS comprise acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis, rhabdomyolysis, hyperlipidemia, and/or fatty liver [19]. Moreover, hyperlipidemia and hyperlactatemia may be risk factors for PRIS [20]. Hyperlipidemia, which was observed in our vitro experiments using fasted rats, may increasethe incidence of PRIS. Apart from hyperlipidemia, these features were not seen in the present animal experiments because the duration of propofol administration was only three hours.

In other animal experiments using rabbits, primary deterioration such as metabolic acidosis was evident at 21 ± 3.2 hours after the onset of propofol infusion [21]. Most clinical diagnoses of PRIS involve prolonged propofol infusion (more than 48 hours) [22] [23]. Differences in metabolic rates among species may also result in differing incidences of PRIS. Further experiments involving longer infusions and different animal models may be necessary to elucidate this.

CPT1, which is the enzyme existing at the outer mitochondria membrane, combining carnitine and acyl-CoA, derived from long-chain fatty acids by acyl-CoA synthetase. The combined acylcarnitine can be transported across the inner mitochondrial membrane [24]. Although propofol inhibits the effects of CPT1 and FFA transport into mitochondria, a sufficient supply and plasma concentration of carnitine may prevent this inhibitory effect, as shown in our study.

There are several limitations to the present study. We only investigated the effects of a relatively short period of propofol administration (three hours). We used animal test subjects and the metabolism of FFA, glucose, and amino acids may differ in humans, especially in fasted states or starvation, because humans may have evolved protective mechanisms against fasting or hypoglycemia. Although we could show that L-carnitine improved propofol-induced increased

triglyceride concentrations in the liver, we were unable to demonstrate fatty liver tissue under histology, fatty liver being a characteristic finding in PRIS.

In addition, we could not clarify directly whether propofol administration had other effects such as metabolic acidosis, arrhythmias, cardiac failure, and rhabdomyolysis in the setting of PRIS, including the inhibitory effects of L-carnitine on PRIS. Further studies are needed to elucidate the mechanisms of action involved in PRIS and how administration of L-carnitine impacts upon this.

5. Conclusion

Propofol inhibits the metabolism of FFA and β oxidation in the mitochondria. Though this is compensated chiefly by glucose metabolism and partially by amino acid utilization for energy production, administration of L-carnitine may improve propofol-induced inhibition FFA metabolism while helping to maintain mitochondrial function.

Conflict of Interest Statement

None authors or institute has received any financial or material support from the manufacture.

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