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The protective effect of L-carnitine on hepatic ischemia-reperfusion injury in rats

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Background/aims: *Ischemia-reperfusion injury may occur during liver transplantation and remains a serious concern in clinical practice. This study was designed to study the potential benefit of L-carnitine on experimental warm hepatic ischemia-reperfusion injury in rats.* ***Materials and Methods:*** *Forty-five male Wistar Albino rats were divided into three groups; Group 1 sham-operation without ischemia-reperfusion (n=15); Group 2, ischemia-reperfusion (n=15); and Group 3, which was administered L-carnitine (200 mg/kg, intraperitoneal, for 4 days) prior to ischemia-reperfusion (n=15). The study animals were then sacrificed to obtain hepatic tissue and serum samples. Tissue levels of malondialdehyde and reduced glutathione and serum levels for aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase were assessed.* ***Results:*** *Mean aspartate aminotransferase levels were significantly higher in Group 2 (405.2 U/L) when compared to Groups 1 (137.1 U/L) and 3 (267.6 U/L). Mean alanine aminotransferase levels were significantly higher in Group 2 (257.1 U/L) when compared to Groups 1 (37.2 U/L), and 3 (118.1 U/L) (p<0.001 for each). Mean lactate dehydrogenase levels were significantly higher in Group 2 (2943.8 U/L) when compared to Groups 1 (1496.5 U/L), and 3 (2185.3U/L) (p<0.001 for each). Mean malondialdehyde levels were significantly higher in Group 2 (54.3 nmol/g) compared to Groups 1 (41.0 nmol/g) and 3 (42.1 nmol/g) (p<0.001 for each). Mean reduced glutathione levels were significantly lower in Group 2 (5.9 nmol/mg) and Group 3 (7.4 nmol/mg) compared to Group 1 (9.1 nmol/mg) (p<0.001 for each).* ***Conclusions:*** *In conclusion, our data supports a protective effect of L-carnitine against oxidative damage in hepatic ischemia-reperfusion injury in rats. This is evidenced by improvement of the antioxidant defense system and lipid peroxidation levels.*

Key words: L-carnitine, hepatic ischemia-reperfusion injury, rats, antioxidant, lipid peroxidation

Karaciğerin deneysel iskemi-reperfüzyon modelinde L-Karnitinin oksidatif hasardan koruyucu rolü

Amaç: *İskemi-reperfüzyon hasarı klinik pratikte karaciğer nakli ile ilgili ciddi bir komplikasyon olmaya devam etmektedir. Bu çalışma, sıçanlarda deneysel hepatik iskemi-reperfüzyon hasarı üzerine L-karnitinin etkisini değerlendirmek için tasarlanmıştır.* ***Gereç ve Yöntem:*** *Toplam 45 erkek Wistar albino rat (262-322 gr) 3 gruba ayrıldı. Grup 1: sham operasyonu yapılan kontrol grubu (n=15), Grup 2: iskemi-reperfüzyon grubu (n=15), Grup 3: karnitine 200 mg/kg intraperitoneal 4 gün uygulandıktan sonra iskemi-reperfüzyon uygulanan grup (n=15). Sham operasyonu ya da iskemi-reperfüzyon ardından, sıçanlar karaciğer doku ve serum örnekleri elde etmek için dekapite edildi. Malondialdehit ve indirgenmiş glutatyon doku düzeyleri ile serum aspartat aminotransferaz, alanin aminotransferaz alanin aminotransferaz ve laktat dehidrogenaz düzeyleri ölçüldü* ***Bulgular:*** *Ortalama (SD) aspartat aminotransferaz değerleri Grup 2 (405.2(103.5)U/L) için Grup 1 (137.1(32.4)U/L) ve Grup 3'den (267.6(56.6)U/L); ortalama (SD) alanin aminotransferaz değerleri Grup 2 (257(97.7)U/L) için Grup 1 (37.2(6.6)U/L) ve Grup 3'den (118.1(46.7)U/L); ortalama (SD) laktat dehidrogenaz değerleri Grup 2 (2943.8(166.1)U/L) için Grup 1 (1496.5(274.8)U/L) ve Grup 3'den (2185.3(258.7)U/L); ortalama (SD) doku malondialdehit düzeyleri Grup 2 (54.3(2.8)nmol/gr) için Grup 1 (41.0(1.4)nmol/gr) ve Grup 3'den (42.1(3.8)nmol/gr) anlamlı olarak yüksek bulunmuştur (herbiri için p<0.001). Ortalama (SD) doku indirgenmiş glutatyon düzeyleri Grup 2 (5.9(0.5)nmol/mg) için Grup 3 (7.4(0.4)nmol/mg) ve Grup 1'den (9.1(0.6)nmol/mg) anlamlı olarak düşük bulunmuştur (herbiri için p<0.001).* ***Sonuç:*** *Bizim verilerimiz L-karnitinin antioksidan savunma sistemi ve lipid peroksidasyon düzeylerini iyileştirerek oksidatif hasara karşı koruyucu etki gösterdiğini ortaya çıkarmıştır.*

Anahtar kelimeler: L-karnitin, hepatik iskemi-reperfüzyon hasarı, antioksidan, lipit peroksidasyonu

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INTRODUCTION

Hepatic blood supply cessation is a common maneuver used to reduce intraoperative blood loss during liver resection. While this is very effective it has also been associated with poor post-operative hepatic function secondary to ischemia-reperfusion injury (I/R). Ischemia-reperfusion injury occurs secondary to cellular damage in a hypoxic organ and is accentuated following restoration of oxygen delivery after long durations of ischemia (1-2).

Hepatic I/R injury has been considered a major cause of both initial poor function and primary non-function of liver allograft after transplantation (3-4). Measures to minimize the adverse effects of I/R injury would be very benefical to patients undergoing transplant and help to improve allograft survival and function. The exact signaling pathways and chemical mediators that occur in I/R injury have yet to be completely identified, but we do know they are quite complex(4-6). Free oxygen radicals that are produced immediately after reperfusion play a pivotal role in ischemia–reperfusion injury (2). Prior animal studies found that prevention of oxygen radical pooling via administration of free radical scavengers has been beneficial Current therapeutic strategies such as ischemic preconditioning or pharmacologic interventions to increase the ischemic time period without resultant liver damage during hepatic surgery focus on prevention of the formation of reactive oxygen species (ROS) have not been conclusive(4-5).

L-carnitine (β-hydroxy-γ-N-trimethylammonium-butyrate) is a essential cofactor in the transport of long-chain fatty acids from the cytosol to mitochondria for subsequent β-oxidation and production of cellular energy. L-carnitine is a natural substance that has been tested for the prevention of liver damage induced by I/R injury (7-9). L-carnitine is known to play a role in membrane modulation, stabilization, and has anti-apoptotic effects by suppressing the mitochondrial permeability and stabilizing free radicals. (9-12). Administration of L-carnitine or its derivatives were documented to improve I/R injury of the heart, kidney, skeletal muscle, and brain (3, 13-16).

The protective effects of L-carnitine against I/R injury in the liver is not well documented as it has been in for other organ systems such as heart and kidney. Therefore, this study was designed to evaluate the effect of L-carnitine on experimental warm hepatic ischemia-reperfusion (I/R) injury in rats. Our work was undertaken was to determine whether L-carnitine exerts cytoprotective properties against ROS-induced cell death in rat hepatocytes.

METHODS

Animals

Male Wistar-Albino rats (262-322 g) were housed in an air-conditioned room at a constant temperature of 22±2 °C with 12:12 h light/dark cycle and fed a standard diet and water ad libitum. Only water was provided in the 18 hours preceding the experiments. Experimental protocol was approved by the Baskent University Faculty of Medicine Animal Care and Use Committee (Project no: DA99/011).

Experimental groups

Rats were divided into three groups. Group 1 (n-15) was the control group and no operation was performed. Group 2 (n=15) underwent ischemia-reperfusion injury, and Group 3 (n=15) was administered carnitine followed by ischemia-reperfusion. I/R injury was induced by creating 60 min of ischemia followed by 2 h reperfusion before hepatectomy. In Group 3, carnitine (Carnitene, Santa Farma, 1g/5 ml ampul) was administered for 4 days (200 mg/kg, intraperitoneal) prior to I/R injury.

Surgical operations

All procedures were performed with the animals under anesthesia (90 mg/kg ketamine and 10 mg/kg chlorpromazine; intramuscularly). An abdominal midline incision was used to perform a hepatectomy. Total hepatectomy was performed after I/R in groups 2 and 3 and immediately in group 1. To induce I/R injury the portal vein was occluded for 60 min and then subjected to reperfusion for 2 h. One rat in group 2 and 2 rats in group 3 died during the I/R period and were excluded from the study.

Biochemical analysis

The animals were sacrificed after 2 hours of reperfusion; blood samples were drawn from the suprahepatic vena cava by a fine needle, then centrifuged at 3000 rpm for 3 minutes and kept at -70 °C until analysis of serum. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) levels were measured in this study. Liver tissue samples obtai-

ned from each animal were stored at -86 °C for the analysis of malondialdehyde (MDA) and glutathione (GSH) levels.

Measurement of serum AST, ALT and LDH levels

Serum LDH, AST and ALT levels were determined spectrophotometrically using an automated analyzer.

Hepatic malondialdehyde and reduced glutathione analysis

Hepatic protein concentration was measured using the method described by Lowry et al (17). For measurement of MDA and reduced GSH, tissue samples were homogenized with ice-cold 0.15 M Potassium Chloride. The MDA levels were assayed for products of lipid peroxidation by monitoring thiobarbituric acid reactive substance (TBARS) formation as described previously by Buege and Aust (18). Lipid peroxidation was expressed in terms of MDA equivalents using an extinction coefficient of 1.56×105 M-1 cm-1 and the results are expressed as nmol MDA/g wet tissue. Glutathione measurements were performed using a modification of the Ellman procedure (19). Briefly, after centrifugation at 2000 g for 10 min, 0.5 ml of supernatant was added to 2 ml of 0.3 mol/l $Na_2HPO_4 \cdot 2H2O$ solution. A 0.2 ml solution of dithiobisnitrobenzoate (0.4 mg/ml 1% sodium citrate) was added and the absorbance at 412 nm was measured immediately after mixing. Glutathione levels were calculated using an extinction coefficient of 1.36×105 M-1cm-1. The results are expressed in nmol GSH/g tissue.

Statistical Analysis

Statistical analysis was performed using computer software (SPSS version 10.0, SPSS Inc. Chicago, IL, USA). Data was expressed as mean (standard deviation; SD). ANOVA and post-hoc Duncan tests were used for the analysis of data and p- value <0.05 was considered statistically significant

RESULTS

Serum AST, ALT and LDH levels

Mean (SD) AST levels were significantly higher in Group 2 (405.2(103.5) U/L) when compared to Group 1 (137.1(32.4) U/L), and Group 3 (267.6(56.6) U/L) (p<0.001 for each; Table 1). Mean (SD) ALT levels were significantly higher in Group 2 ((257.1(97.7) U/L) when compared to Group 1 (37.2(6.6) U/L), and Group 3 (118.1(46.7) U/L) (p<0.001 for each; Table 1). Mean (SD) LDH levels were significantly higher in Group 2 (2943.8(166.1) U/L) when compared to Group 1 (1496.5(274.8) U/L), and Group 3 (2185.3(258.7) U/L) (p<0.001; Table 1). While highest values for AST, ALT and LDH were identified in Group 2, levels obtained in Group 3 were also higher than group 1 (p<0.001, Table 1).

Hepatic malondialdehyde and glutathione levels

Mean (SD) MDA levels were significantly higher in group 2 (54.3(2.8) nmol/g) when compared to Group 1 (41.0(1.4) nmol/g), and Group 3 (42.1(3.8) nmol/g) (p<0.001 for each; Table 2). Mean (SD) reduced GSH levels were significantly lower in Gro-

Table 1. Serum AST (U/L), ALT (U/L) and LDH (U/L) levels in the control (group 1), I/R (group 2) and carnitine+I/R (group 3) groups

	Group I (Control)	Group II (I/R)	Group III (Carnitine+I/R)
	Mean (SD)	Mean (SD)	Mean (SD)
AST levels (U/L)	137.1 (32.4)	405.2 (103.5)*	267.6 (56.6)**
ALT levels (U/L)	37.2 (6.6)	257.1 (97.7)*	118.1 (46.7)**
LDH levels (U/L)	1496.5 (274.8)	2943.8 (166.1)*	2185.3 (258.7)**

*p<0.001; compared to group 1 and group 3. **p<0.001; compared to group 1.

Table 2. Hepatic total protein, malondialdehyde (MDA) and reduced glutathione

	Group I (Control)	Group II (I/R)	Group III (Carnitine+I/R)
	Mean (SD)	Mean (SD)	Mean (SD)
Malondialdehyde (MDA) (nmol/g)	41.0 (1.4)	54.3 (2.8)*	42.1 (3.8)
Reduced glutathione (GSH) (nmol/mg)	9.1 (0.6)	5.9 (0.5)**	7.4 (0.4)**

*p<0.001; compared to group 1 and group 3. **p<0.001; compared to group 1.

up 2 (5.9(0.5) nmol/mg) and Group 3 (7.4(0.4) nmol/mg) when compared to Group 1 (9.1(0.6) nmol/mg) ($p<0.001$ for each; Table 2).

DISCUSSION

Identification of hepatic dysfunctions via increased levels for serum AST, ALT and LDH in the I/R groups indicates that I/R was successfully induced. While being higher than control group, significantly lower levels of serum markers for liver function in the carnitine plus I/R group compared with I/R rats without carnitine suggest a protective effect of carnitine on liver function. Similarly, L-carnitine was reported to significantly restore the changes in enzyme activities (AST, ALT and GGTP) due to its antioxidant effect and its ability to act as a radical scavenger. This allows for protection of membrane permeability in radiation induced hepatic oxidative damage (8).

Liver hypoxia in severe hepatic I/R injury results in ischemic hepatitis associated with pericentral liver hypoxia characterized by a dramatic rise in serum aminotransferase (1). In prior studies the effects of exogenous L-carnitine on lipid peroxidation and tissue damage in models of I/R injury in rats, significantly higher levels of ALT and AST was reported to indicate the success of the experimental model. A decrease in serum aminotransferases with L-carnitine administration indicated attenuation of the liver damage (9). It has been suggested that L-carnitine act as free- radical scavenger, and protect cells from reactive oxygen species (ROS) (7). Previous studies have described antioxidant properties of carnitine in ageing atherosclerotic rats, hypercholesterolaemic rabbits; HIV-1-infected subjects and in preventing renal functional deterioration due to ischemia/reperfusion (7).

Besides being is an absolute requirement for the transport of activated long chain acyl units into the mitochondria, L-carnitine also protects against ROS by acting as an antioxidant scavenging hydroxyl radicals and inhibiting hydroxyl radical formation by the Fenton reaction system (20). Accordingly, L-carnitine administration was shown to raise glutathione levels in ischemic and aged rats and the energy enhancing action of L-carnitine has been accused for the increase in glutathione status after L-carnitine supplementation. Several authors have demonstrated glutathione-promoting action of L-carnitine to support this notion (7, 21), prior studies have shown a carnitine dependent reduction in activities of GSH-P and a increase in those of GSH-Red in the liver. Our findings suggest a significant reduction in tissue GSH levels in the I/R group. This further suggests the role of oxidative stress in the I/R injury of hepatic tissue (7). Although carnitine did not completely deplete GSH, there was a tendency towards higher values for reduced GSH in the rats in group 3 when compared to Group 2. A carnitine dependent reduction in activities of GSH-peroxidase while increasing those of GSH-Red in the liver indicate the role of oxidative stress in the I/R injury of hepatic tissue (7).

L-carnitine facilitates the uptake of acetyl-CoA into the mitochondria during fatty acid oxidation, enhances acetylcholine production, and stimulates protein and membrane phospholipids synthesis. L-carnitine has antioxidant activity towards oxidative stress via an inhibition of the increase in lipid hydroperoxidation (22). Lipid peroxidation is thought to be one of the most important consequences of excessive free radical production that play a significant role in the mechanism of I/R injury by damaging structural and functional properties of cellular organelles (7). The basic mechanism leading to cellular death is induced by lipid peroxidation in several studies with TBARS levels (do not abbreviate), expressed in MDA equivalents, reflecting the severity of the lipid peroxidation (7). Increased levels of MDA, the principle product of lipid peroxidation, occurs in I/R rats without carnitine administration indicates the successful inhibition of lipid peroxidation in the rats administered carnitine prior to I/R injury (Group 3).

In an experimental hepatic ischemia-reperfusion injury model in rats, significantly higher level of MDA was present in serum and liver tissue in the I/R group. Administration of L-carnitine at different time periods of the ischemia-reperfusion procedure was documented to make no significant alteration in plasma MDA levels (9). Similarly, a dose dependent, superoxide scavenging capacity of carnitine with a decrease of lipid peroxidation in liver, heart and kidney ischemia/reperfusion was reported with an increase of MDA concentration in the venous effluent after reperfusion (7). Mitochondrial proteins could be the target for hepatic toxicity leading to the loss of energy production and cellular ion control (23). The action of L-carnitine in mitochondrial energy production is to facilitate the transfer of long-chain fatty acids from cytosol to mitochondria, thereby playing an impor-

tant role in the production of ATP (24). Indeed, L-carnitine was shown to increase ATP production in the myocardium in cisplatin-induced cardiomyopathy (25). Mitochondria have been shown to be the source of the intracellular superoxide ion. The positive effects of carnitine on mitochondrial functions are thought to reduce the mitochondrial superoxide ion production followed by a limited amount of intracellular reactive oxygen radicals leading maintenance of high GSH levels as well as inhibition of lipid peroxidation (26-27). Dysfunction is a energy-dependent metabolic pathways and transport mechanisms due to loss of mitochondrial respiration and subsequent reduction in ATP production was shown to be the leading factor in I/R injury (26-27).

Accordingly, GSH has been the key component for the protective effects of GSH-supplemented Perfadex® solution on early allograft function as well as indication of GSH preconditioning as a potential regime to prevent mitochondrial injury in the setting of pulmonary I/R (27-28).

In the present study, serum AST, ALT and LDH levels were increased following I/R injury indicating that cellular damage occurred and liver function decreased. The increases in lipid peroxidases, serum and liver MDA accompanied by a significant reduction in GSH levels are markers of oxidative liver damage. L-carnitine pretreatment may potentially protect from I/R induced hepatotoxicity. This protective effect is based on improvement in GSH depletion as and restoration to control levels for MDA.

Recently, Li et al. reported that elevated expression of Peroxisome proliferator-activated receptors which are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily are involved in energy homeostasis and play an important part in the protective effect. This might contribute to the amelioration of lipid homeostasis the improvement of antioxidant ability, and increased ATP in L-carnitine treated cells (29).

In conclusion, our data reveals a protective effect of L-carnitine supplementation on oxidative damage in hepatic I/R injury in rats. This is evidenced by the improvement of antioxidant defense system and lipid peroxidation levels. When administered prior to I/R injury, L-carnitine protected cellular membranes against oxidative stress via stimulating positive effects on mitochondrial ATP production and stimulation of membrane phospholipids and protein production. Future studies concerning the role of time and the nature of ischemia in relation to relative contribution of intracellular versus vascular oxidant stress to hepatic I/R injury are needed to clarify the mechanisms responsible for ROS generation in liver I/R injury.

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