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REVIEW

L-Carnitine and Potential Protective Effects Against Ischemia-Reperfusion Injury in Noncardiac Organs: From Experimental Data to Potential Clinical Applications

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ABSTRACT

The mechanism of ischemia-reperfusion (I/R) injury is complex and multifactorial. In this condition, systemic event results in morbidity and mortality in several pathologies, including myocardial infarction, ischemic stroke, acute kidney injury, trauma, and circulatory arrest. Hypoxia over ischemia phase leads to energy imbalance and changes of cellular homeostasis and functional or structural alterations. In addition, during the reperfusion period, some events, including calcium influx, release of intracellular enzymes, and cell membrane integrity breakdown, cause cell death. L-carnitine (LC) and its derivatives have been suggested to improve tolerance against I/R injury in various tissues. The favorable effects of LC are possibly mediated by its antioxidant and anti-inflammatory effects or by other capability due to increase in the intracellular carnitine content. In this article, anti-ischemic properties of LC and its derivative in noncardiac organs are reviewed using relative animal and human research. Although most of the studies on noncardiac internal organs have shown protective effects of LC administration against I/R injury, more clinical trials are needed to clarify the clinical importance of LC as a treatment option for I/R-induced injury.

KEYWORDS

acetyl carnitine; in vitro; in vivo; ischemia reperfusion injury; L-carnitine; reactive oxygen species

Ischemia/reperfusion injury

Ischemia/reperfusion (I/R) injury is a momentous pathological systemic event whereby organ damage occurs by restoration of blood and oxygen supply to hypoxic tissues following a period of deprivation (Tano and Gollasch, 2014). Indeed, tissue insult directly depends on the magnitude and period of blood supply interruption during ischemia. Over the prolonged ischemia, due to lack of oxygen delivery, anaerobic metabolism for adenosine triphosphate (ATP) production takes place, leading to intracellular pH reduction and lactate accumulation. Then, by lack of ATP availability, ion transport pumps collapse and result in intracellular and mitochondrial calcium accumulation. Calcium entry leads to swelling, rupture, and finally death of the cells. Such injury is frequently happening in clinical conditions such as myocardial infarction, stroke, and peripheral vascular diseases (Eltzschig and Eckle, 2011).

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Resuming the reperfusion of obstructed vessels is essential to ameliorate the ischemia-induced insult; paradoxically, however, by resuming the consumption of oxygen upon the reperfusion phase, ischemia injury exacerbates due to overproduction of reactive oxygen species (ROS) and infiltration of proinflammatory neutrophils. Following reperfusion, leukocyte recruitment will happen via ROS release and the chemoattractants. Leukocytes worsen the damage area both directly by their cytotoxic effects and indirectly by the occlusion of microvascular circulation (Zimmerman and Granger, 1994).

The pathologic events conducted by I/R injury increase the mitochondrial permeability due to production of transition pores, a common pathway for devastating events (Kalogeris et al., 2012). Hence, reperfusion injury is another limiting factor for interventional therapy such as organ transplantation (Parks and Granger, 1986).

Although not all organs have equal susceptibility to ischemic events, the mainstay of all therapeutic approaches to ischemia resolution is prompt restoration of blood flow and oxygen delivery. In addition, applying a preconditioning agent prior to I/R induction has been suggested to be helpful in preserving cell survival.

Among these preconditioning agents, several physiological and pharmacological free radical scavengers such as L-carnitine (LC) (Moghaddas and Dashti-Khavidaki, 2016), N-acetyl cysteine (NAC) (Mohammad et al., 2014), Vitamin E (Sirmali et al., 2015), and so on have been proposed to be effective in management of I/R injury. For example, in myocardial I/R events, such as coronary bypass surgery or angioplasty, vitamin E and NAC, as an antioxidant thiol-containing compound, have been proved to prevent adverse effects of ROS when they were used as preconditioning agents (Dhalla et al., 2000).

L-carnitine

L-carnitine (g-trimethylamino-b-hydroxybutyrate) is a naturally endogenous agent that exists in mammalian cells as its unesterified form. The most famous derivatives, esters, include acetyl-L-carnitine (ALC), propionyl-L-carnitine (PLC), and palmitoyl-L-carnitine.

The main source of LC and its derivatives is dietary products, especially meat and dairy, and to a lesser extent, endogenous biosynthesis (Moghaddas and Dashti-Khavidaki, 2016), mainly in liver and kidney (Moghaddas and Dashti-Khavidaki, 2016; Rebouche, 1992).

L-carnitine acts as a co-transporter of long-chain free fatty acids from cytosol into mitochondria. The mitochondria consumes these long-chain free fatty acids for β-oxidation and acetyl coenzyme A (CoA) production during the tricarboxylic acid cycle. The mitochondrial reactions produce ATP in the electronic transport chain and oxidative phosphorylation process, which consume a high degree of oxygen instead. At the end, water will be produced by reduction of oxygen, and ROS formation will be inhibited (Moghaddas and Dashti-Khavidaki, 2016).

On the other hand, LC can potentiate the activity of antioxidant enzymes, including glutathione peroxidase, catalase, and superoxide dismutase (SOD). It can also chelate ROS-generation's metal ions (e.g., ferrous). The antioxidant activity is similar to that of other standard antioxidant agents such as alpha-tocopherol (Gülçin, 2006).

The exact beneficial effects of LC and its derivatives on the human organism are not fully understood. Some highly energy-demanding tissues such as skeletal and cardiac muscles as well as reproductive tissue are rich with LC (Dayanand et al., 2011).

It is believed that the most protective effect of LC and its derivatives against I/R injury arises from antioxidant activity, which can alleviate I/R injury by inhibition of ROS production in aerobic metabolism.

The aim of this article is to provide a review of the probable protective effects of LC and its derivatives as well as the possible protective mechanisms against I/R insult. Our focus is on existing evidence in vitro, in vivo, or in human studies of noncardiac organs. We have excluded the protective effects of LC on neuromuscular and cardiac organs during I/R injury due to previously published evidences (Ferrari et al., 2004; Moghaddas and Dashti-Khavidaki, 2016).

L-carnitine and retinal ischemia/reperfusion injury

Some reports have declared that I/R injury plays an important role in retinal diseases such as glaucoma, diabetic retinopathy, and age-related macular degeneration. The mechanism of the cell death induced by retinal ischemia is not completely understood. It is suggested that cellular energy failure and glutamatergic stimulation initiate a destructive cascade involving neuronal depolarization, calcium influx, and oxidative stress, resulting in ischemic retinal injury. However, compared to many organs, such as the brain, the retina exhibits a remarkable natural resistance to ischemic injury, which reflects its peculiar metabolism and unique environment. LC's esters enhance optic nerve growth and increase visual function. In addition, LC and its esters are capable of protecting the chaperone activity of α-lens crystalline, which is a water-soluble protein found in the lens and cornea of the eyes, helping in transparency of objects. They can also decrease posttranslational modifications induced by oxidative stress and prevent cataract formation (Osborne et al., 2004; Szabadfi et al., 2010). Despite significant concentrations of LC in various ocular tissues, there is a paucity of literature regarding the role of LC in this organ. In the literature review, only three animal studies and one in vivo study evaluated the protective effects of LC against I/R-induced retinal injury (Alagoz, 2002; Derin, Aydin, et al., 2006; Kocer et al., 2002; Shamsi et al., 2007).

Two similar studies in guinea pigs showed that I/R-induced retinal thickness is significantly alleviated by LC pretreatment in animal model. LC exerted a significant neuroprotective effect on retina when it was administered before transient I/R insult, possibly by decreasing lipid peroxidation (Alagoz, 2002). Koçer et al., (2002) also confirmed the results during histopathological investigation. Interestingly, LC could prove its efficacy on chronic restraint stress as well. During stressful conditions, lipid peroxidation and the generation of free radicals will be stimulated, and pretreatment with LC significantly controls the harmful effects.

Results of intervention showed that retina levels of thiobarbituric acid reactive substances (TBARS) significantly increased, and SOD as well as catalase activities significantly decreased, in the restraint stress condition. LC pretreatment significantly prevented lipid peroxidation and stress-induced alterations in visually evoked potentials but did not alleviate SOD level and catalase activities (Derin, Aydin, et al., 2006).

An in vitro study on the effects of LC against oxidative changes in human retinal pigment epithelium (RPE) cells, a kind of safeguarding photoreceptor cell that prevents various stress-induced changes in retinal tissue, was performed by Shamsi et al. (2007) This study showed that LC protected the RPE cells by inhibiting the peroxide-induced cytopathic effects. LC treatment partly alleviated oxidant-induced cell death and could complement the cellular defense system, while it was a safe and nontoxic compound.

On the other hand, retinal aging occurs during the metabolic processes in which H_2O_2 is produced from electron leakage of superoxide and hydroxyl radicals from the mitochondria.

This in vivo study is worth mentioning because LC protective effects were seen in H_2O_2-induced morphologic changes as they happen in reality (Shamsi et al., 2007). The details of all studies are summarized in Table 1.

Table 1. A summary of studies of potential protective effects of L-carnitine against organ ischemia/reperfusion injury.

Study	Model of study	Involved organ	LC dose and route of administration	Monitoring indices	Results
Alagoz et al. (2002)	Guinea pigs	Retina	LC 100 mg/kg i.p. repeated in 5 doses before ischemia induction	Histological investigation (thickness of retinal tissue) and MDA values	Reduction in tissue thickness, amelioration in MDA level
Kocer et al. (2002)	Guinea pigs	Retina	LC 500 mg/kg i.p. before ischemia induction	TBARS assay and histological investigation	Reduction in tissue thickness, amelioration in TBARS level
Derin, Aydin, et al. (2006)	Male Wistar rats	Retina	LC 50 mg/kg/day by gavage before 21 days (1 h/day) chronic restraint stress	Visual evoked potentials, histochemical analysis, TBARS levels, SOD and catalase activity, and protein determination	No significant effect on SOD and no effect on catalase activity but amelioration in other indices
Shamsi et al. (2007)	Human retinal pigment epithelium	Retina	LC at the concentration of 25, 50, 75, 100, and 250 μM in the presence or absence of 100 μM H_2O_2	RPE-antioxidant enzymes, GSH and SOD, morphologic change, cell death assessment by MTT	Death protection of RPE cells, increase in GSH and SOD activities
Stroh et al. (1998)	Sprague-Dawley rats	Intestine (splanchnic artery)	PLC 200 mcg/kg i.v. 2 min before reperfusion	MPO activity, survival rate and time, endothelial function	Increase in survival time, attenuation in hematocrits, increases in tissue MPO activity and splanchnic artery endothelial dysfunction
Akin et al. (2007)	Wistar albino rats	Intestine	Sodium nitroprusside 5 mg/kg i.p. or LC 500 mg/kg i.p. after induction of ischemia	Tissue MDA and histopathologic examination	Similar positive effect of LC and sodium nitroprusside in histological and inflammatory factors
Hosgorler et al. (2010)	Wistar albino rats	Intestine	LC 200 mg/kg i.v. 2 min prior to the 3-h reperfusion	Level of MDA, NO in tissue and blood, collagen levels, bursting pressures, and histopathologic changes	Lower morphological damage, amelioration in other indices
Yuan et al. (2011)	Sprague-Dawley rats	Intestine	LC 80 mg/kg i.v. before reperfusion injury	levels of TNF-α, IL-1β, IL-6, and IL-10, histological evaluation, and bacterial translocation	Enhancement in IL-10, suppression in serum TNF-α, IL-1β and IL-6, reduction in levels of bacterial translocation and morphological damage
Derin et al. (2004)	Wistar rats	Stomach	LC 100 mg/kg i.v. 5 min before ischemia induction	Gastric mucosal injury, acidic mucopolysaccharide content in the gastric mucosa, and TBARS gastric lipid peroxidation, gastric SOD activity, mucosal catalase activity, gastric mucosal GPx, activity and prostaglandin E2	Amelioration of TBARS indices, increase in tissue catalase activity and prostaglandin E2, but no change in SOD activity, GPx activity, and mucus content

Derin, Agac, et al. (2006)	Wistar rats	Stomach	LC 100 mg/kg i.v. 5 min before ischemia induction	Neutrophil accumulation and hemorrhagic lesions in a histological study, MPO activity	Reduction in neutrophil accumulation in ischemic tissue, reduction in gastric injury and MPO activity
Puetz et al. (2001)	Wistar rats	Liver	alphaketoglutarate plus LC hydrochloride 5 mmol/L in preservative solution	Lipid peroxidation assay LDH, ALT, GLDH, histopathological analysis	Abrogation in all indices and histopathological changes
Atila et al. (2002)	Lewis rats	Liver	LC 200 mg/kg i.p. 3 h before ischemia induction	AST, ALT, GGT levels, liver tissue, and serum carnitine	Lowering in all enzymes and improvement in histological studies
Yonezawa et al. (2005)	Wistar rats	Liver	LC 100 mg/kg i.v. 30 min before ischemia reduction	microcirculation TNF-α, lipid peroxidation, ATP measurement, histomorphology, and TUNEL staining	No significant differences in all indices
Canbaz et al. (2007)	Wistar rats	Liver	LC 200mg/kg i.v. 2 hours before total warm hepatic ischemia/reperfusion	MDA, MPO level of both plasma and liver tissue, total antioxidant capacity, ALT and AST levels in plasma, and histopathologic examination	Decrease in lipid peroxidation and significant increase in total antioxidant capacity
Çekın et al. (2013)	Wistar albino rats	Liver	LC 200 mg/kg i.p. for 4 days prior to ischemia induction	MDA, GSH, serum levels for AST, ALT and LDH, histopathological studies	Amelioration in all parameters
Ergün et al. (2001)	Albino rabbits	Kidney	LC 100 mg/kg i.v. 20 min before ischemia induction	Histological changes, tissue and serum TBARS and MDA levels	Amelioration in all indices
Mister et al. (2002)	Sprague-Dawley rats	Kidney	PLC or LC 3.6 mg/mL i.v. infusion, for cold ischemia solution PLC 1.2 mg/ml added during 4 hours before transplantation	Histological examination, tissue adenine nucleotides, MDA, LDH	Amelioration in all indices, GFR preservation, no change in ATP levels
Görür et al. (2005)	Wistar rats	Kidney	LC 100 mg/kg i.p. before ischemia induction	Tissue MDA level, MPO activity, and NOx level	Reduction in MPO, MDA, and NO level
Azzollini et al. (2008)	Lewis to Brown Norway rat	Kidney	PLC 1.2 mg/ml added to Belzer solution supplemented during cold ischemia	Histological examination, lipid peroxidation, iNOS expression, and protein nitration	Decrease in lipid peroxidation, iNOS expression, and protein nitration, amelioration in histological changes and post-transplant-induced ATN
Ye et al. (2010)	Human proximal tubule epithelial cell	Kidney	LC at concentration of 1, 10, 50, 100, 200, 500, 1,000 μM for 12 h	ROS production, lipid peroxidation, antioxidant defensive system, mitochondrial dysfunction and DNA damage through caspase 3 activity, Bcl-2 and Bax expression, cytochrom-c release	Inhibition of H_2O_2-induced cell viability loss, intracellular ROS generation, and lipid peroxidation, only with the concentration ranging from 10 to 100 μM; amelioration of total antioxidative capacity of GPX, catalase, and SOD, cell apoptosis inhibition

(*Continued on next page*)

Table 1. (Continued)

Study	Model of study	Involved organ	LC dose and route of administration	Monitoring indices	Results
Liu et al. (2012)	Sprague-Dawley rats	Kidney	LC solution 250 mg/ml (2 ml/kg i.v.) at 30 min before reperfusion	Antioxidant enzymatic activity and phospholipase A2 and SOD activity, MDA level	Reduction in lysophospholipids, free fatty acids, and nitrotyrosine, amelioration in MDA, SOD, and phospholipase A2 activity
Idrovo et al. (2012)	Sprague-Dawley rats	Kidney	LC 250 mg/kg or 5-Aminoimidazole-4-carboxyamide ribonucleoside 30 mg/kg, or combination of both drugs	Tissue carnitine, ATP, MDA levels, carnitine palmitoyltransferase I activity and serum levels of TNF-α, histopathological analysis	Combination of two drugs increased CPT1 activity and ATP levels and reduced renal MDA and serum TNF-α levels, ameliorated histological changes
Rabie et al. (2012)	Albino rabbits	Kidney	LC 200 mg/kg i.p. and LC plus either ramipril (1 mg/ kg p.o.) or losartan (10 mg/kg i.p.) before ischemia induction	Tissue TNF-α content, MPO, LDH, SOD activity, histological evaluation, kidney carnitine, GSH, and NOx levels	LC alone or combined with either agent ameliorated all markers as compared with ramipril or losartan monotherapy
Dokmeci et al. (2007)	Wistar albino rats	Testis	LC 500 mg/kg i.p. 30 min before applying torsion	Tissue MDA, histopathological examination, Johnsen's spermatogenesis criteria, and mean seminiferous tubule diameter measurements	Attenuation in histological changes and other indices
Shalaby and Afifi (2008)	Albino rats	Testis	LC 500 mg/kg i.p. 30 min before reperfusion	Histological, histochemical, and immunohistochemical studies for Bcl-X and testosterone Ab-1	Attenuation in histological changes and other indices
Guan et al. (2009)	Sprague-Dawley rats	Testis	LC 500 mg/kg i.p. 2 h after torsion induction	Tissue MDA and heat HSP70, SOD, catalase, and GPx evaluation; Histopathological finding and germ cell apoptosis indices	Increase in HSP70, amelioration in histological changes and other indices
Mohamed (2011)	Albino rats	Testis	LC 100 mg/kg i.p. 1 h before detorsion	immunohistochemical study, endothelial nitric oxide synthase assays	Protective effects on immunohistochemical changes
Usta et al. (2008)	Sprague–Dawley rats	Ovary	LC 100 mg/kg i.p. 30 min before 24 h reperfusion induction	Histopathology studies, tissue MDA and serum IL-6 levels, HIF-1α antibody	Attenuation in histological changes and other indices increased by ischemia

ALC = acetyl L-carnitine; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATN = acute tubular necrosis; ATP = adenosine triphosphate; CK = creatine kinase; CoA = coenzyme A; CPT1 = carnitine palmitoyltransferase I; EDL = extensor digitorum longus; F2-iso = F2-isoprostanes; GFR = glomerular filtration rate; MTT = [3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide]; GGT = gamma glutamyl trnspeptidase; GLDH = glutamate dehydrogenase; GPx = glutathione peroxidase; GPLC = glycine propionyl- L-carnitine; GSH = glutathione; HIF-1α = hypoxia inducible factor-1 alpha; H_2O_2 = hydrogen peroxide; HPS70 = heat shock protein 70; IL = interleukin; iNOS = inducible nitric oxide synthase; i.p. = intraperitoneal; I/R = ischemia/reperfusion; i.v. = intravenous; LC = L-carnitine; LDH = lactate dehydrogenase; MDA = malondialdehyde; MPO = myeloproxidase; NAC = N-acetyl cycteine; NO = nitric oxide; NOx = nitrate/nitrite concentrations; PC = protein carbonyl; PLC = propionyl L-carnitine; p.o. = per os (by mouth); ROS = reactive oxygen species; RPE = retinal pigment epithelium; SOD = superoxide dismutase; SOL = soleus; TBARS = thiobarbituric acid reactive substances; TNF-α = tumor necrosis factor-α.

As a result, LC action in the retina is mostly described as antioxidant activity, inhibition of oxidative changes, and redistribution of antioxidant enzymes in the tissues. It is probably useful for clinical application of age-related ocular complications.

L-carnitine and gastrointestinal ischemia/reperfusion injury

I/R-induced intestinal injury happens following abdominal aortic aneurysm surgery, small bowel transplantation, cardiopulmonary bypass, strangulated hernias, neonatal necrotizing enterocolitis, and septic or hypovolemic shock (Collard and Gelman, 2001; Moore et al., 1994; Swank and Deitch, 1996). The intestine, as a metabolically highly active organ, is among the most sensitive organs to I/R injury. Even though the exact mechanisms of intestinal I/R injury have not been completely defined, it seems that mediators of oxidative stress, polymorphonuclear neutrophils (PMN), and bacterial translocation play important roles. Some researchers have focused on the application of antioxidants such as allopurinol, deferoxamine, N-acetylcysteine (NAC), ethanol, ascorbic acid, tocopherol, pentoxifylline, captopril, and verapamil for enhancing the tolerance of the intestine during reperfusion injury (Collard and Gelman, 2001; Mallick et al., 2004; Moore et al., 1994; Swank and Deitch, 1996). Oxidative stress has an important role in I/R-induced gastric injury as well (Hassan et al., 1997).

I/R injury remains a main limiting step for success of liver transplantation. Organ recovering insult leads to higher incidence of acute or chronic rejection after transplantation.

Hence, inhibiting the adverse consequences of I/R injury would not only ameliorate transplantation outcomes, but also lessen the mortality rate. The mechanism of liver IR injury is still undefined (Zhai and Kupiec-Weglinski, 2011).

In general, I/R insult to the transplanted liver is a multifaceted process that combines elements of "warm" and "cold" injury. The process of warm organ damage, occurring in situ in low flow states, is dominated by Kupffer cell–derived cytotoxic molecule-mediated hepatocellular injury. Cold I/R injury, experienced during ex vivo preservation, is mostly caused by damage to the liver sinusoidal endothelial cells and disruption of the microcirculation. These seemingly distinct processes share common mechanisms and overlapping effects on nonparenchymal (Kupffer cells/lymphocytes) and parenchymal (hepatocytes) cell functions, both of which lead to organ failure (Glantzounis et al., 2005; Zhai and Kupiec-Weglinski, 2011). Antioxidant therapies such as using SOD derivatives, thiol compounds, selective nitric oxide (NO) synthase inhibitors, and peroxynitrite decompositors have been examined for their ability to alleviate liver I/R injury (Glantzounis et al., 2005; Zhai and Kupiec-Weglinski, 2011). There are also some studies on the effects of LC against I/R injury of the gastrointestinal tract; three animal studies evaluated the effects of LC derivatives against I/R-induced intestinal injury; two animal studies evaluated the effects of LC derivatives against I/R-induced gastric injury; and two in vitro and five animal studies evaluated the effects of LC derivatives against I/R-induced hepatic injury (Akin et al., 2007; Atila et al., 2002; Çekın et al., 2013; Derin, Agac, et al., 2006; Derin et al., 2004; Hosgorler et al., 2010; Puetz et al., 2001; Stroh et al., 1998; Tolba et al., 2003; Yuan et al., 2011).

L-carnitine and intestinal ischemia/reperfusion injury

In a comparative study, the protective effects of sodium nitroprusside, as an NO donor, and LC were examined in an experimental model of I/R-induced intestinal injury. This study declared the same alleviative effects for LC and sodium nitroprusside against I/R-induced histological and inflammatory changes (Akin et al., 2007).

Evidence showed the positive effects of LC on a long duration of reperfusion in intestinal organ model (Hosgorler et al., 2010). LC preapplication was able to reduce the severity of reperfusion injury by significant reduction in morphologic changes ($p = .03$), the number of perfused microvessels ($p = .008$), and epithelial regeneration ($p = 0.05$) in comparision with the control group (Hosgorler et al., 2010).

Yuan et al. (2011) evaluated the effects of LC on the labeled E-coli-fed rats suffering from I/R injury of the small intestine. This study focused on bacterial translocation from the mesenteric lymph nodes, liver, spleen, and portal vein and inflammatory cytokines. Results indicated that bacterial translocation was higher in the I/R group compared to the LC-administrated group. LC-treated rats had enhancement in serum levels of anti-inflammatory cytokines such as interleukin- (IL-) 10 and suppression in production of serum inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 compared to untreated rats ($p < .05$). LC treatment also improved I/R-induced pathological impairment in small intestine (Yuan et al., 2011). As mentioned, I/R injury to the small intestine causes local production of ROS, degranulation of intestinal mucosal mast cells, and release of inflammatory mediators such as histamine and TNF-α (Andoh et al., 2001). On the other hand, I/R insult results in decrease in ATP production and mucosal cell energy exhaustion. All these events can be alleviated with LC pretreatment.

L-carnitine and gastric ischemia/reperfusion injury

Two animal studies by Derin and colleagues (Derin et al., 2004; Derin, Agac, et al., 2006) assessed the effect of LC against I/R-induced impairment of the gastric mucosal barrier. The first study indicated that LC pretreatment reduced I/R-induced gastric mucosal lesions and lipid peroxidation and ameliorates I/R-induced decline in gastric tissue catalase activity and prostaglandin E2 production (Derin et al., 2004). The second study showed that LC pretreatment before gastric ischemia induction significantly reduced to 12.7 2.06 mm^2 ($p < .05$ versus I/R group) and myeloperoxidase (MPO) activity reduced to (12.55 0.81 U g^{-1} protein, $p < .05$ compared to the nontreated I/R group). They suggested that LC provides marked protection against gastric I/R injury through its ability to reduce neutrophil accumulation in the ischemic tissue (Derin, Agac, et al., 2006). Although these results are promising, further evaluations and clinical studies on humans are needed to clarify the clinical protective role of LC in gastric mucosa as well as other parts of the gastrointestinal system.

L-carnitine and hepatic ischemia/reperfusion injury

Stroh et al., (1998) assessed the effect of PLC on pancreatic and hepatic cell damage following splanchnic I/R injury. Administration of PLC before reperfusion increased tissue survival time and survival rate. Pretreatment alleviated tissue MPO activity and had positive effects on splanchnic artery endothelial dysfunction. The authors suggested that inhibition of leukocyte infiltration into intestinal tissue, preserving endothelial function, decreasing microvascular permeability, and maintaining tissue perfusion as possible mechanisms of PLC protective effects (Stroh et al., 1998).

Interestingly, addition of LC to the preservation fluid could reduce the injury associated with cold-ischemic preservation of fatty livers. It has been suggested that LC has a potent effect as a metabolic supplement for graft survival after being preserved. While reperfusion of cold-stored fatty livers entails massive destruction of hepatic mitochondria, LC supplementation remarkably mitigates changes and leads to significant reduction of the parenchymal enzyme leakage from reperfused liver. Release of alanine aminotransferase was reduced to one-third

(127 22 vs. 423 61 U/L), and the loss of glutamate dehydrogenase in the perfusate reduced significantly (42 7 vs. 542 134 U/L) when compared with livers stored in controlled condition. Results obtained from in vitro study demonstrated that LC supplementation in preservative fluid is a novel approach for the safe and more successful preservation of ischemia-sensitive steatotic liver graft. Of note, steatotic liver graft is not a well-qualified tissue for transplantation and has a higher risk of a nonfunctional graft (Puetz et al., 2001; Tolba et al., 2003).

There are also positive results on the effect of exogenous LC administration before ischemia induction in warm hepatic I/R injury (Yonezawa et al., 2005).

For example, a Japanese group conducted a study for checking this capability on warm hepatic I/R injury. Although they found that LC supplementation improved hepatic blood flow during the reperfusion period, they could not elucidate the protective effects of LC on hepatic warm I/R injury. Their results showed that plasma levels of liver enzymes and inflammatory cytokines were not significantly different between LC-treated and nontreated animals at 1 hour after reperfusion and even more at 24 hours after reperfusion (Yonezawa et al., 2005).

On the contrary, LC suplementation revealed beneficial effects against lipid peroxidation when administered before warm hepatic ischemia (Canbaz et al., 2007; Çekın et al., 2013).

Moreover, the potential role of exogenous LC in preventing I/R damage in the liver resection procedure was assessed in animal study. Results indicated that LC administration resulted in preservation of liver enzymes (aspartate aminotransferase, alanine aminotransferase, gama-glutamyl transpeptidase). These enzymes are indicators of hepatocellular injury, and they were significantly lower in the LC-treated rats ($p < .001$). (Atila et al., 2002)

Animal evidence favors LC pretreatment prior to liver resection; however, the data must be confirmed in well-performed clinical trials. Clearly, LC pretreatment has potential protective properties for use in high-risk patients prior to hepatic resection modalities such as central located tumors, extended hepatectomies, and transplantation.

Pretreatment with LC and its derivatives before ischemia induction, especially adding these agents to the tissue preservative solution, may decrease I/R-induced hepatic injury during liver resection/transplantation. The summary of related studies is described in Table 1.

L-carnitine and kidney ischemia/reperfusion injury

Ischemia-reperfusion injury occurs in the kidney in a manner similar to that of other organs and may be considered as an inflammatory or vasomotor phenomenon. Renal ischemia impairs the renal tubular cells by disrupting the vital cellular metabolic machinery. More insult is induced by restoration of blood flow and subsequent generation of free oxygen radicals. Two known clinical events, shock and renal transplantation, expose the kidney to I/R injury (Greene and Paller, 1990; Grekas et al., 1996; Kelly et al., 1994; Paller, 1992; Rabb et al., 1996). Injury is initiated by the lack of oxygen during kidney cold ischemic period and is augmented by ROS generation during subsequent warm reperfusion of the graft through activation of the inflammatory cascade. Increased ROS generation after kidney transplantation may participate in or progress chronic renal allograft nephropathy (Ye et al., 2010).

Ischemia/reperfusion is one of the most important causes of acute kidney injury (AKI). Some evidence has demonstrated the ATP depletion and activation of multiple enzyme systems, including proteases, inducible nitric oxide synthase (iNOS), phospholipases, SOD, peroxidases, and catalases. They are responsible for cell dysfunction and eventually cell death in the kidney. On the other hand, it has been thought that phospholipase A2 which catalyzes the hydrolysis of fatty acids and other agents such as ROS, plays an important role in I/R associated cell injury (Edelstein et al., 1997; Goligorsky et al., 2002; Haq et al., 1998; Kribben et al., 1994). Antioxidants may allow better preservation of graft function and ameliorate

the associated injury by reducing oxidative stress in kidney and inhibiting the apoptotic cell death (Edelstein et al., 1997; Goligorsky et al., 2002; Haq et al., 1998; Kribben et al., 1994). There are seven animal studies and one in vitro research on the protective effects of LC as an antioxidant against I/R-induced kidney injury; all have been summarized in Table 1 (Azzollini et al., 2008; Ergün et al., 2001; Idrovo et al., 2012; Liu et al., 2012; Mister et al., 2002; Rabie et al., 2012; Ye et al., 2010).

Ergün et al. (2001) suggested that LC pretreatment may be a good option for minimizing the complications of I/R condition in shock states, surgical processes, and organ transplantation. Its protective effects refer to prevention in histological changes such as marked edema and congestion and decrease in lipid peroxidation; however, this idea must be evaluated in a clinical setting (Ergün et al., 2001). Other researchers believe that decreasing lipid peroxidation, neutrophil function, and nitric oxide metabolism are the most likely protective mechanisms that are responsible for the beneficial effects of LC on I/R-induced injury in the kidney (Görür et al., 2005). They have also suggested that LC has a direct antioxidant effect, promotes endogenous antioxidant defense, and inhibits the cell apoptosis (Liu et al., 2012; Ye et al., 2010).

Preserving organs in cold storage fluid is always a matter of interest. The potential protective effects of LC have been established in cold preservation fluid as described in the hepatic injury section. This issue has been assessed in a comprehensive study conducted in 2005. The study was performed in an isolated perfused kidney, which already had injury. The aim of this study was to explore whether addition of PLC during cold storage of the donor kidney prevents I/R injury and facilitates immediate graft function. Data revealed that pre-ischemia exposure of kidneys to PLC largely prevented renal function impairment in the isolated perfused kidney. Histologic findings in the PLC-administrated group showed very mild post-ischemic kidney lesions compared with untreated ischemic kidneys. Adding PLC to organ preservation solution during cold ischemia largely preserved the organ as compared to untreated ischemic grafts. Furthermore, addition of PLC to Belzer UW solution prevented PMN cell graft infiltration and reduced tubular injury in the first hours after transplantation, which may be attributed to I/R protection. These new achievements will probably be important in posttransplant delayed graft function treatment modalities (Mister et al., 2002).

Delayed graft function after kidney transplantation is mostly affected by peritransplant I/R injury. In addition, graft injury due to I/R might amplify the response of T cells to alloantigen, facilitating allograft rejection. Accordingly, the beneficial effects of PLC in reducing I/R injury in an allogeneic kidney transplant setting, a setting that more closely mimics the clinical condition, were evaluated. A model of kidney graft I/R injury was established in the fully mismatched Lewis to Brown Norway rat. For preventing acute rejection, recipient rats were treated with cyclosporine A (10 mg/kg/day intramuscularly) (Mister et al., 2002).

Kidney tissues in transplant solutions containing PLC were healthier and resulted in lower posttransplant serum creatinine levels and decreased lipid peroxidation and iNOS expression. Histological data after transplantation showed that PLC significantly inhibited tubular necrosis ($p < .01$) and neutrophil infiltration of the allografts ($p < .05$) and led to improvement of three-month graft survival ($p < .05$). The results suggest that immunosuppression with cyclosporine A did not hamper the action of PLC to protect the graft against I/R damage (Azzollini et al., 2008). Efficacy of PLC on I/R injury modulation during transplantation must be tested in human organ transplantation.

In the following, we summarize two important studies conducted to evaluate the nephroprotective effects of LC on I/R injury.

Idrovo et al. (2012) focused on cell death in I/R condition due to cellular homeostasis disruption and energy depletion. As is obvious, fatty acids are a major energy source in the kidneys. Part of the study was related to introducing carnitine palmitoyltransferase I (CPT1), a mitochondrial membrane enzyme that utilizes LC to transport fatty acids to mitochondria for β-oxidation process and ATP generation during I/R injury. Carnitine palmitoyltransferase I activity is regulated indirectly by adenosine monophosphate (AMP) and directly by 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR). The authors hypothesized that administration of LC and AICAR could reestablish the energetic balance after reperfusion and ameliorate renal I/R injury. Results favored the combination treatment with LC and AICAR, which significantly improved the survival rate after I/R injury. The combined treatment significantly increased CPT1 activity and ATP levels and lowered renal malondialdehyde (MDA) and serum TNF-α concentration. All events led to improvement in renal histomorphology and reduction in serum creatinine as well as blood urea nitrogen (BUN). It is worth mentioning that administration of each agent per se did not show any significant improvement in most of the measurements (Idrovo et al., 2012).

Research by Rabie et al. (2012) evaluated the nephroprotective effect of LC in combination with angiotensin antagonists on I/R injury. Angiotensin antagonists have the well-known side effect of acute worsening of renal function at their initial use. Results showed that I/R exerted deleterious effects on kidney function via enhancing the production of oxidative stress and inflammatory biomarkers and decreasing LC level in the kidney. On the other hand, both ramipril and losartan induced significant worsening of kidney function tests. Meanwhile, the drugs alleviated raised oxidative and inflammatory markers as compared with the I/R-controlled group. LC alone or combined with either angiotensin antagonist agent ameliorated all oxidative and inflammatory markers as compared to ramipril (1 mg/kg orally) or losartan (10 mg/kg intra peritoneal) monotherapy. This study opened a new perspective for the use of LC in the treatment of renal diseases associated with AKI caused by other nephrotoxic agents or LC-deficiency induced AKI (Rabie et al., 2012).

L-carnitine and testis/ovaries ischemia/reperfusion injury

I/R injury in the testis has mostly been reported during testicular torsion, a urological syndrome caused mainly by a twist in the spermatic cord. Mammalian testes are highly sensitive to oxidative damage. Testicular torsion and detorsion-induced I/R insult is associated with overgeneration of ROS and reactive nitrogen species and can result in permanent injury and infertility. Events occurring during testicular I/R injury are the same as those observed in other organs. It seems that damage from reperfusion is more severe than that induced by ischemia. However, mechanisms responsible for testicular damage have not yet been fully clarified. Some proposed mechanisms during testicular I/R include elevation of ROS production, activation of mitogen-activated protein kinases, and induction of transcription of growth factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and vascular endothelial growth factor, triggering apoptotic machinery and generation of several inflammatory cytokines. This pathologic cascade results in testicular atrophy and impairs spermatogenesis.

Therefore, there is a strong need to identify specific pharmacological treatment to limit the damage triggered by I/R procedures. Several pharmacological antioxidative agents such as SOD, catalase, allopurinol, melatonin, selenium, caffeic acid phenethyl ester, resveratrol, NAC, and garlic extract have been reported as therapeutic agents for the management of testicular

torsion and may be useful to ameliorate the sequelae of this disease (Agarwal et al., 2003; Dokmeci et al., 2007; Wilhelm Filho et al., 2004).

Dokmeci et al. (2007) showed that the testicular MDA level increased during torsion (ischemia) and mostly during detorsion (reperfusion). Pretreatment with LC before testicular torsion prevented increase in MDA levels and attenuated histological changes (Dokmeci et al., 2007). LC ameliorated severe proapoptotic affection induced by I/R in the spermatogenic cells and the leydig cells (Shalaby and Afifi, 2008).

Other researchers have also established the antioxidant and antiapoptotic effects of LC against testicular I/R injury (Guan et al., 2009). In another rat model of torsion/detorsion–induced testicular I/R injury, LC-pretreated animals exhibited fewer degenerative features and unremarkable changes in endothelial nitric oxide synthase compared with the untreated testicular I/R injury group (Mohamed, 2011).

Ovarian torsion is a rare but serious health problem. Usta et al. (2008) detected response to LC administration in ovaries that were subjected to torsion/detorsion. LC infusion before reperfusion decreased total tissue damage scores and tissue MDA levels. Damage to the ovarian tissue peaked in the ischemia group and significantly weakened after 24 hours of reperfusion. Histopathological changes and tissue MDA levels decreased more prominently in the LC-treated group (Usta et al., 2008).

Taken together, all studies indicated that the preoperative use of LC alleviates I/R-induced toxic effects, possibly through its antioxidant activity and inhibitory effect on germ cell apoptosis.

The use of LC in animal model was successful in preserving germ cell mass and preventing infertility after testicular I/R injury. Although there is very limited data for ovarian torsion and detorsion, hopeful results have been released. Before drawing any conclusions regarding use in humans, further well-controlled, carefully designed clinical studies are needed. Table 1 summarizes the effect of LC on I/R injury in testes and ovaries.

Future direction

The first definition of ischemia, lack of blood supply due to obstruction of arterial inflow, was presented in the early nineteenth century (Kalogeris et al., 2012). After that, studies were conducted to find the underlying mechanisms of I/R injury and develop therapies to limit the devastating effects of disorders (Kalogeris et al., 2012). Over the past 30 years, impressive research has described the molecular, cellular, and systemic events that occur during ischemia per se. Of note, most of our findings supporting the concept that, paradoxically, reperfusion may exacerbate tissue injury and necrosis were made early in this period. This new discovery has provided a vast research area for introducing therapeutic agents with the aim of reducing tissue injury (Khanna et al., 2005; Scarabelli and Gottlieb, 2004). Organs committed to apoptosis and death might be reversibly insulted; the idea of rescuing much of the cells is borne out by applying the various interventions, such as ischemic preconditioning, protein kinase C modulation, cytochrome P450 inhibitors, and pretreatment with antioxidants, which induced substantial reduction in necrotic and apoptotic cell death in the experimental models of I/R injury (Scarabelli and Gottlieb, 2004). There are still challenges in discovering how reperfusion is mediated or how proposed agents can be prevented or treated. Despite much investigation and discovery, we are still far from understanding the exact I/R mechanisms and alleviating interventions.

The first report of LC discovery in muscle tissue was made one hundred years ago (Stephens et al., 2007). Today, we know that total LC content in normal conditions is in cardiac and

skeletal muscles (98% of total), liver and kidney (1.6% of total), and extracellular fluid (0.4% of total) (Atila et al., 2002).

In the body, LC has several vital metabolic roles; the most documented is the role in displacing long-chain fatty acids into the inner of mitochondria. The event is necessary for β-oxidation reaction as well as energy production. LC also has beneficial effects on fatty acid turnover. It is reported that the peroxidation of fatty acid in ischemic tissue leads to generation of free oxygen radicals which directly interfere to oxidative damage of cellular macromolecules such as nucleic acids, proteins, and lipids. (Jones et al., 2010; Malaguarnera, 2012).

During the 20th century, a great enthusiasm developed for evaluating the effects of LC on preventing I/R damages. There are many studies on the protective effects of LC against I/R-induced heart injury, clinically or experimentally (Ferrari et al., 2004; Najafi, 2013), While, these reports also included other organs. We looked at these noncardiac interventions comprehensively; we aimed to introduce a new scope to manifest the future perspectives of LC's protective effects against I/R injury of noncardiac organs. In our previous works, we successfully showed that LC and its derivatives have beneficial effects against I/R injury in central nervous system and muscular tissues in animal studies and some human studies (Moghaddas and Dashti-Khavidaki, 2016).

The protective effects of LC are attributed to reduction of stress by either scavenging ROS or improving antioxidant systems, such as SOD and GSH/GPx (Jones et al., 2010).

For example, although in this article, most of the studies were performed in animal model, they were well able to show the possible mechanisms involved in I/R injury protection. From the proposed mechanisms, ameliorating catalase activities of enzymes such as SOD, MDA, and MPO; alleviating anti-inflammatory cytokines; inhibiting leukocyte infiltration; preserving endothelial function; decreasing microvascular permeability; and maintaining histopatological changes are the most suggested.

The limitation of the review for reaching a comprehensive conclusion is that most of the evidence originates from animal and in vitro cellular models. Lack of clinical study makes it difficult to prove the protective effects of LC and its derivatives in human models. Most of the studies, however, demonstrate the beneficial effects of LC administration against I/R. They have been manifested by prophylactic administration of LC before ischemia induction.

Adding LC to organ preservation solutions before transplantation also showed promising results regarding organ protection against cold-ischemic damages and reducing the risk of delayed graft function.

Most research used LC and its derivatives as a supplementation regimen, but routine supplementation in the clinical setting must be considered with caution. Of note, LC is not merely a cofactor in β-oxidation, but rather it has many known and yet to be discovered functions in physiology.

Another clear limitation is the diversity of methodologies that have been used in animal studies. For example, there were differences in the methods of inducing I/R in animal models. In actual clinical conditions, a long perfusion period routinely happens after a surgical procedure, but in an experimental model, most studies used a 2- to 3-hour reperfusion time before data gathering. (See Table 1) Hence, future studies are necessary to provide more information focusing on the late period of reperfusion after ischemia induction.

On the other hand, each study had a different technique for indicating the loss of organ integrity after inducing I/R. For example, some studies evaluated the vascular permeability, (Hosgorler et al., 2010), some assessed the bacterial translocation (Yuan et al., 2011), and most considered leukocyte infiltration (Derin, Agac, et al., 2006) or tissue damage biomarkers and oxidative stress biomarkers (Rabie et al., 2012). We highly recommend designing a series of

studies with homogeneity in methodology regarding LC dose and route of administration and I/R indication criteria in both animal and human studies. Before any LC application, it must be considered that all experimental animal models have been designed to yield informative results by limiting the duration of ischemia and by utilizing young, healthy, and genetically homogeneous animals, not real conditions in humans.

Demonstration of organs salvaged by any intervention is more challenging in the clinical setting; nevertheless, identification of potential targets that can achieve organ salvage after ischemia raises hope that reduction of necrotic size and postischemic complications is a clinically attainable goal. However, large randomized, multicenter, clinical trials are still needed to reconfirm the efficacy of these interventions. Nonetheless, the research in this field is intense and the future is highly promising.

Conclusion

I/R exerted deleterious effects on organ functions mostly via enhancement in the generation of oxidative stress and inflammatory biomarkers as well as interference in energy storage. The favorable effects of LC are possibly mediated by its antioxidant and anti-inflammatory effects or by other capability to increase the intracellular carnitine content. Subsequently, improvement in mitochondrial oxidative phosphorylation and energy production happen. Administration of LC and its derivative in animal study could demonstrate the protective effects on I/R injury. Our knowledge about the role of LC in human models is very limited. LC's place in animal studies, especially in transplantation of solid organs such as kidney and liver, is outstanding; So far, it can be used in organ transplantation and other potential clinical utilization. However, results are conflicting and other studies must be considered. Taking all results together, the protective effects of LC in different ischemia conditions such as surgeries, organ transplantation and shock state has been confirmed in animal studies but before any judgment in clinical condition, performing well-designed clinical trials with large population is crucial.

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