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L-carnitine inhibits ethanol-induced gastric mucosal injury in rats

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Abstract:
L-carnitine is a quaternary amine that is essential for the normal oxidation of long-chain fatty acids by mitochondria. It is known that L-carnitine and its derivatives prevent the formation of reactive oxygen species, scavenge free radicals and protect cells from peroxidative stress. Oxygen-derived free radicals and lipid peroxidation products play a critical role in the pathogenesis of ethanol-induced gastric mucosal injury. The aim of the present study was to determine the effect of L-carnitine on lipid peroxidation induced by ethanol in the rat stomach. In our study, gastric mucosal injury was induced by the intragastric administration of 1 ml of absolute ethanol. Test compounds were given to rats by gavage 30 min before the ethanol administration. The animals were killed 60 min after the administration of ethanol. The stomach of each animal was removed. Mucosal damage was evaluated by macroscopic examination, histological analysis and by measurement of lipid peroxidation and glutathione activity. The intragastric administration of ethanol induced hyperemia and hemorrhagic erosions in the rat stomachs. L-carnitine significantly prevented gastric ulcerogenesis induced by ethanol and decreased the ulcer index. Plasma and gastric lipid peroxidation that was increased significantly by ethanol was decreased after treatment with L-carnitine. Ethanol treatment decreased significantly the gastric glutathione levels, and pretreatment with L-carnitine increased them significantly. Based on these data, the beneficial effects of L-carnitine on ethanol-induced gastric mucosal injury may be attributed to its antiperoxidative effects.

Key words:
carnitine, ethanol, gastric mocosal injury, lipid peroxidation

Abbreviations: ANOVA – analysis of variance, H&E – hematoxylin and eosin, TBARS – thiobarbituric acid reactive substances

Introduction

Peptic ulcer is one of the common diseases affecting man. Severe stress, *Helicobacter pylori* infection and ingestion of alcohol, aspirin and other non-steroidal anti-inflammatory drugs are predisposing factors. Recently, studies have implicated the generation of oxygen-derived free radicals in the pathogenesis of gastric ulcers [23, 39]. Furthermore, it has been shown that lipid peroxidation plays an important role in the pathogenesis of gastric mucosal lesions induced by ethanol [36]. Antioxidants are known to inhibit lipid peroxidation and scavenge free radicals [5, 19, 23]. Hence, there is a need to develop drugs that are capable of scavenging these free radicals and which produce beneficial effects against gastric ulcers.

L-carnitine is a small, water-soluble molecule important in mammalian fat metabolism. It is essential for the normal oxidation of fatty acids by the mitochondria and is involved in the trans-esterification and excretion of acyl-CoA esters, the oxidation of branched chain α-ketoacids, and removal of potentially toxic acylcarnitine esters from mitochondria. L-carnitine is present in both plasma and tissue as free carnitine or bound to fatty acids as acylcarnitine derivatives [29]. It is known that L-carnitine and its derivatives prevent the formation of reactive oxygen species, scavenge free radicals and protect cells from peroxidative stress [4, 16, 22, 26, 34]. It is, therefore, possible that L-carnitine could scavenge free radicals and produce beneficial effects against gastric mucosal ulcer. Hence, we hypothesized that L-carnitine, because of its antiperoxidative and scavenger effects, may be useful to prevent ethanol-induced gastric mucosal injury.

Materials and Methods

Animals and reagents

Male Sprague-Dawley rats weighing 200–250 g were used in the experiments. They were housed at 22 ± 1°C under a 12 light/12 h dark cycle and had free access to standard pellet diet for rats and tap water. The rats were deprived of food for 24 h before experimentation, but were allowed free access to drinking water. The experimental protocol was approved by Trakya University Animal Care and Use Committee. All chemicals were purchased from Sigma Chemical (St. Louis, Mo. USA).

Gastric damage induced by ethanol

Gastric hemorrhagic lesions were induced by intragastric administration of 1 ml of absolute ethanol to each rat. L-carnitine (500 mg/kg) and saline were given intragastically 30 min prior to administration of ethanol. The animals were killed 60 min after the administration of ethanol [19]. The stomach of each animal was then removed, opened along the greater curvature, and rinsed with physiological saline. Thereafter, it was mounted on a paraffin plate to minimize mucosal folding. The gastric mucosa was carefully examined macro- and microscopically, and scored.

Macroscopic evaluations

It was assessed by grading the gastric injury (macroscopic damage score) on a scale from 0 to 4, based on the severity of hyperemia and hemorrhagic erosions: 0 – almost normal mucosa; 0.5 – hyperemia; 1 – one or two lesions; 2 – severe lesions; and 3 – very severe lesions; and 4 – mucosa full of lesions [11]. The eroded gastric mucosal areas were measured using a transparent sheet with one millimeter square scale and a dissecting microscope. The damaged part was expressed as the percentage of the whole glandular area. Enhancement or inhibition of ethanol-induced hemorrhagic injury was given as a percentage in comparison to the control.

Histopathological evaluations

In the groups treated with 500 mg/kg of L-carnitine and ethanol + saline (six rats in each group), three samples from comparable region of each stomach were excised and routinely processed followed by paraffin embedding. Sections (5 μm thick) were stained with hematoxylin and eosin (H&E) and examined under a light microscope. One-centimeter lengths of each histological section were divided into three fields. Each field was scored histologically on a 0–4 scale according to previously described criteria: 0 – normal; 1 – epithelial cell damage; 2 – glandular distruption, vasocongestion or edema in the upper mucosa; 3 – mucosal distruption, vasocongestion or edema in the mild-lower mucosa; 4 – extensive mucosal distruption involving the full thickness of the mucosa [14]. The overall mean value of the scores for each of the fields was taken as the histological ulcer index for that section. All determinations were performed in a randomized manner and histological sections were coded to eliminate an observer bias.

Determination of glutathione and lipid peroxide levels

Tissue samples were homogenized with ice-cold 150 mM KCl in a tissue homogenizer. Homogenized tissue samples were centrifuged at 3000 rpm for 15 min at 4°C. Supernatant was removed and recentrifuged at 15000 rpm for 8 min. Glutathione measurements were

performed using Ellman procedure [13]. Lipid peroxidation was quantified by measuring the formation of thiobarbituric acid reactive substances (TBARS) as described previously by Ohkawa et al. [25]. Lipid peroxide levels were expressed in terms of malondialdehyde equivalents.

Statistical analysis

All measurements were done in a blinded fashion on pre-coded samples. Data analysis was carried out with SPSS 10.0 Windows program package. Macroscopic damage score and histological ulcer index in stomach were evaluated by Kruskal-Wallis test followed by the Mann-Whitney *U*-test. GSH parameters, lipid peroxidation levels and the total area of mucosal lesions were analyzed with one-way analysis of variance (ANOVA) followed by Tukey's test for multiple comparisons. The results are presented as the mean ± SEM and differences were considered significant for $p < 0.05$.

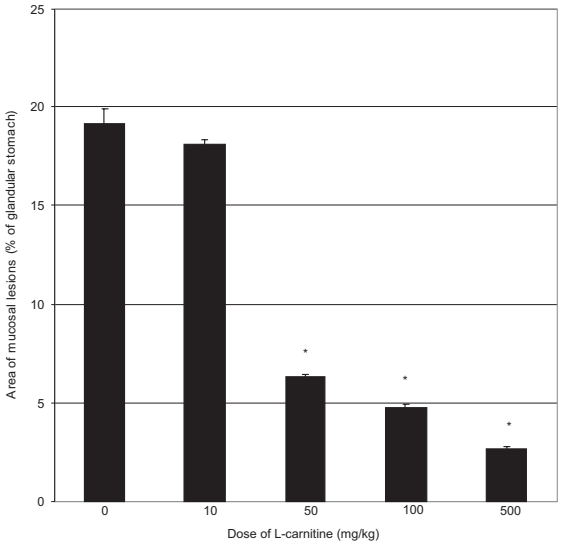

Fig. 1. Effect of increasing doses of L-carnitine on acute gastric mucosal injury induced by ethanol in rats. L-carnitine was given to the rats by gastric intubation 30 min before the ethanol administration. Values are reported as the mean SEM of four to six rats. * $p < 0.05$ compared to the ethanol + saline-treated group

Results

Effect of L-carnitine on ethanol-induced gastric mucosal injury

Neither saline alone nor L-carnitine alone produced any macroscopic lesions in the rat stomachs. In the rats treated with ethanol + saline, multiple erosions and bleeding developed in the glandular stomach 1 h after ethanol administration. In contrast, pretreatment with L-carnitine 30 min before the ethanol administration inhibited the gastric erosions in a dose-dependent manner (Fig. 1). In addition, repeated treatment with L-carnitine (500 mg/kg) for 7 days resulted in smaller erosions induced by ethanol, and the degree of the inhibition was similar to the acute treatment (data not shown). Therefore, in the following experiments, we used L-carnitine at the dose of 500 mg/kg and examined its pharmacological action. L-carnitine at a dose of 500 mg/kg dramatically reduced the size of the erosions (Fig. 2). The protective effect of L-carnitine was confirmed histologically. Ethanol administration resulted in large areas of epithelial crypt loss, predominantly neutrophilic infiltrate throughout the mucosa and submucosa, erosion, and mucosal bleeding. In contrast, pretreatment with L-carnitine

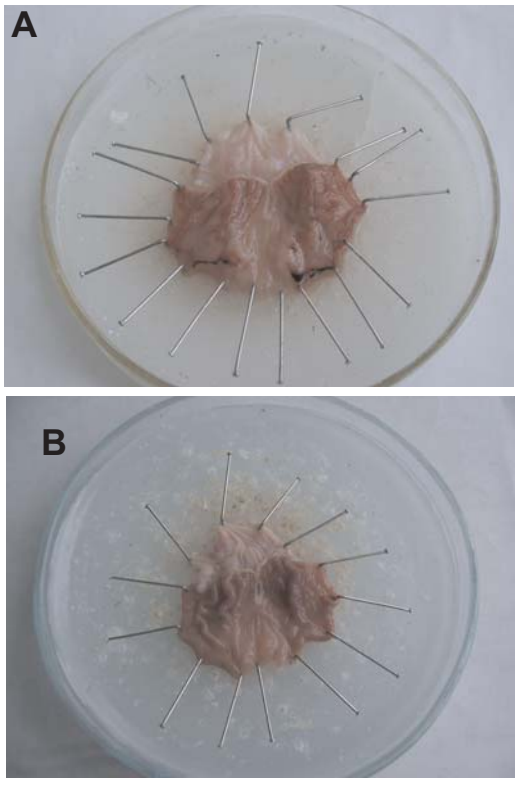

Fig. 2. Effect of L-carnitine on acute gastric mucosal injury induced by ethanol in rats. Multiple hemorrhagic erosions with acute edema developed in the glandular stomach of rats 1 h after administration of ethanol (**A**). The administration of L-carnitine at a dose of 500 mg/kg markedly reduced these hemorrhagic erosions and edematous lesions (**B**)

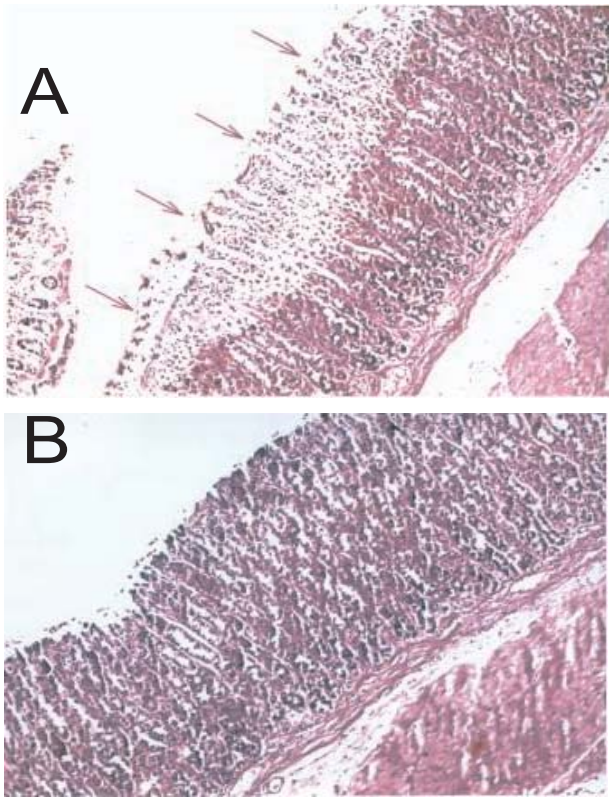

Fig. 3. Effect of L-carnitine on histological features of gastric erosions induced by ethanol in rats. Hemorrhagic mucosal erosions and inflammatory cell infiltrations developed in the glandular stomach of rats 1 h after the administration of ethanol (A). The administration of L-carnitine at dose of 500 mg/kg markedly inhibited these changes (B) (H&E X100)

resulted in smaller erosions with few neutrophils (Fig. 3). The macroscopic and histological gastric injury score increased significantly 1 h after the ethanol treatment. This increase was significantly inhibited by the treatment with L-carnitine (Tab. 1). The total area of gastric erosions in animals receiving vehicle was 19.17 ± 0.76 1 h after ethanol administration. L-carnitine (500 mg/kg) significantly reduced the lesion area by 2.62 ± 0.14 ($p < 0.05$) (Tab. 1).

Effect of L-carnitine on thiobarbituric acid-reactive sustances in the plasma and gastric tissue

Both plasma and gastric lipid peroxidation levels were found to be significantly higher than control in the ethanol + saline group ($p < 0.05$). The increase in TBARS in the plasma and gastric mucosa was inhibited by 500 mg/kg of L-carnitine ($p < 0.05$) (Tab. 2).

Tab. 1. Macroscopic and histological comparison of gastric mucosa between group given only ethanol and group given ethanol following pretreatment with L-carnitine

Treatment	n	% of total mucosal area	Macroscopic damage score	Histological ulcer index
Ethanol + Saline	6	19.17 ± 0.76	3.33 ± 0.21	3.33 ± 0.21
Ethanol + L-carnitine	6	2.63 ± 0.14[a]	0.83 ± 0.11[a]	1.00 ± 0.00[a]

Data are presented as the mean ± SEM of six rats. Gastric mucosal lesions are expressed as a percentage (%) of the total gastric mucosa occupied; macroscopic and histological evaluations were performed according to the criteria of Cashin and Esplugues, respectively. [a] $p < 0.05$ compared with the group given only ethanol

Tab. 2. Effect of L-carnitine on plasma and tissue malondialdehyde and gastric tissue glutathione levels in ethanol-administered rats

Treatment	n	TBARS (plasma) nmol/ml	TBARS (gastric tissue) nmol/g of tissue	Glutathione (gastric tissue) nmol/g of tissue
Control	6	2.84 ± 0.06	5.15 ± 0.45	1.49 ± 0.27
Ethanol + Saline	6	20.95 ± 0.35[a]	26.76 ± 0.76[a]	0.68 ± 0.16[a]
Ethanol + L-carnitine	6	8.16 ± 0.26[b]	12.28 ± 0.76[b]	1.21 ± 0.34[b]

L-carnitine (500 mg/kg) was given to the rats by gavage 30 min before the ethanol administration. Values are expressed as the means ± SEM (n = 6). [a] Significantly different from control group at $p < 0.05$; [b] significantly different from ethanol-treated group at $p < 0.05$

Effect of L-carnitine on glutathione in the gastric mucosa

Gastric glutathione levels were decreased in ethanol + saline group when compared with the control group ($p < 0.05$). L-carnitine (500 mg/kg) pretreatment prevented the ethanol-induced reduction of gastric GSH ($p < 0.05$) (Tab. 2).

Discussion

It has long been known that intragastric administration of ethanol induces congestive hyperemia of the

gastric mucosa and submucosa and that edema, necrosis and hemorrhage may arise in such areas [24], but the detailed mechanism whereby this mucosal damage takes place is still not properly understood. There is growing evidence that oxygen-derived free radicals play a role in the pathogenesis of various disorders of the digestive system such as gastric ulcer [39]. Recently, much attention has been focused on the role of reactive oxygen species, including superoxide, hydroxyl radicals, and hydrogen peroxide in mediating alcoholic tissue damage [36]. Free radical scavengers have a protective effect against gastro-duodenal injury, and levels of these reactive oxygen species can be reduced by antioxidants [23]. It has been demonstrated that by using various antioxidants, such as melatonin [5] and garlic [19], ulcer formation in digestive tract could be decreased. Furthermore, lipid peroxidation mediated by free radicals is believed to be one of the important causes of cell membrane destruction and cell damage, because the cell membrane contains many lipids, especially unsaturated fatty acids [39]. Lipid peroxidation leads to loss of membrane fluidity and impairment of ion transport and membrane integrity on the surface of epithelial cells and helps to generate gastric lesions [6]. It has been demonstrated that the mucosal barrier does not hinder the diffusion of ethanol into the gastric mucosa [30]. Therefore, it might be assumed that the relatively lipophilic ethanol can also be taken up by the cells. Thus, the oxidative metabolism of ethanol may generate free radicals.

Carnitine is a vitamin-like substance that is structurally similar to amino acids. Most carnitine is obtained from diet. It can also be synthesized endogenously by skeletal muscle, heart, liver, kidney, and brain from the essential amino acids lysine and methionine. L-carnitine and its derivatives have several important intracellular functions and they have exhibited many pharmacological effects [29]. Since the carnitine system, which consists of carnitine, carnitine esters, several specific intracellular enzymes, and membrane transporters, plays an important role in the cellular trafficking of short-, medium-, and long-chain fatty acids. Indeed, the carnitine system is involved in the following functions [29]: (1) utilizalion of substrates for energy production at the mitochondrial level; (2) lipid peroxidation at the peroxisomal level, not related to energy production; (3) acylation and deacylation of proteins, such as very low density lipoprotein, at the endoplasmic reticulum level; (4) membrane phospholipid turnover; and (5) maintenance of cell osmotic balance.

In our study, the antioxidative and/or free radical scavenging effects of L-carnitine, which have been proven in many previous studies, was taken as a standard and the gastroprotective action of this compound was investigated. L-carnitine has anti-radical and anti-oxidant effects and scavenges the reactive oxygen species [4, 16, 22, 26, 34]. It has been demonstrated that many pathologic conditions that caused elevation of malondialdehyde due to lipid peroxidation were prevented by carnitine and its derivatives, such as ischemia/reperfusion injury [2, 20, 21, 26], adriamycin- [18, 32] and doxorubicin-induced [22, 33] cardiomyopathy and myocardial infarction [27, 35]. In addition, L-carnitine and its derivatives have also shown anti-inflammatory effects in some models of vascular inflammation in rats [10] and neuroprotective action [9, 37]. Besides, L-carnitine increases the synthesis of phospholipids required for membrane formation and integrity and plays a role in the membrane repair by reacylation of phospholipids [17]. Recently, it has also been suggested that L-carnitine derivatives may reduce the age-dependent accumulation of lipofucsines [4], which are considered to be by-products of lipid peroxidation. Moreover, L-propionyl carnitine, a derivative of L-carnitine, protects erythrocytes and low density lipoproteins against peroxidation induced by oxygen reactive species [7]. Pola et al. [28] showed that propionyl L-carnitine was responsible for the regression of cutaneous ulcers in vasculopathics. Oral L-carnitine has been claimed to aid healing of skin ulcers secondary to vasculopathies and sickle cell leg ulcers. The exact mechanism for these actions is not yet known, but it has been suggested that L-carnitine may exert a direct effect on the membrane. It may prevent cell damage by stabilizing the membrane against free radical-induced injury, and also may prevent mitochondrial injury, thus increasing energy production and decreasing the leakage of free radicals [8, 38]. Furthermore, it has recently been shown that L-carnitine has an antioxidant protective effect on gastric mucosa [16]. Izgut-Uysal et al. have investigated the gastroprotective effect of L-carnitine in rat gastric mucosa following exposure to cold-restraint immobilization. They found that prior administration of L-carnitine could prevent the occurrence of mucosal lesions by interfering with lipid peroxidation that is associated with the oxidative damage

in gastric tissue. Recently, Arafa et al. [3] have reported that carnitine esters, particularly propionyl L-carnitine could protect gastric mucosa from alcohol-induced acute mucosal injury, and this protective effect might be probably induced thorough an anti-radical mechanism. To our knowledge, the role of L-carnitine in ethanol-induced gastric mucosal injury is undefined. In the current study, we examined whether there is a protective effect of L-carnitine on biochemical and histopathologic changes associated with gastric mucosal injury in the rats.

This study was undertaken to evaluate the anti-ulcer activity of L-carnitine. By the same token, the gastroprotective effects of L-carnitine observed in the current study can possibly be mediated through its well-known antioxidant potential. The present study demonstrated for the first time that L-carnitine attenuated ethanol-induced gastric mucosal injury, and significantly inhibited the increase in TBARS production, which is an index of lipid peroxidation, in the plasma 1 h after ethanol administration. Gastric mucosal injury was reduced in the present study by a model in which L-carnitine was given 30 min before ethanol administration. This study indicates that the anti-ulcer activity of L-carnitine may be due to its free radical scavenging activity and cytoprotective effect on gastric mucosa. This result suggests that L-carnitine plays some role in the gastric damage induced by orally administered ethanol.

Studies focusing on the pathogenesis of the ethanol-induced gastric mucosal injury suggest that the initial event is disruption of the vascular endothelium resulting in an increased vascular permeability, followed by vascular stasis and congesion. Furthermore, it is known that ethanol causes edema, vacuolization, and necrosis of the luminal epithelial cells [36]. Our results agree with the results of these studies. L-carnitine dramatically reduced the size of the erosions and histological ulcer index.

It has been reported by many authors that two different effects of L-carnitine may be distinguished. The scavenger effect toward oxygen reactive species has been demonstrated by Ronca et al. L-carnitine inhibits hydroxyl radical production in the Fenton reaction system. L-carnitine may act by chelating iron required for the generation of hydroxyl radicals [31]. On the other hand, the preventive effect of L-carnitine on the formation of oxygen reactive species due to xanthine/XO system has been shown by Di Giacomo et al. [12]. It has also been demonstrated that human volunteers receiving alcohol after treatment with L-carnitine exhibited significantly reduced levels of ethanol in blood that was associated with the increased excretion of acyl-carnitine derivatives [1].

The detection and measurement of lipid peroxidation is the evidence cited to support the involvement of free radicals [23, 36]. The thiobarbituric acid assay is the most popular method to estimate the malondialdehyde level, which is an indication of lipid peroxidation and free radical activity [15]. In this study, there was a significant increase in plasma and tissue malondialdehyde levels in rats. This is consistent with studies [5, 19, 23, 24, 30, 36] that associate the increased lipid peroxidation with gastric ulcers. Moreover, the gastric tissue malondialdehyde levels, higher than those in plasma, were indicative of localized gastric damage. L-carnitine reduced malondialdehyde levels in plasma as well as in the gastric tissue, which correlates with its anti-ulcer effect. This is consistent with its reported antioxidant effect [4, 16, 22, 26, 34].

In summary, it has been shown that L-carnitine has the antioxidative and/or free-radical scavenging effects and the drug is effective in some conditions induced *via* oxidative stress. Even though the antioxidant and/or free radical scavenging mechanism of action of L-carnitine awaits elucidation, the results obtained by us indicate that L-carnitine modifies ethanol-induced elevation of oxidative reactions. However, only two studies have been performed to determine its effect on gastric ulcer. Our findings suggest that L-carnitine has the gastro-protective activity and agree with other studies [3, 16]. Hence, L-carnitine is a promising anti-ulcer drug in peptic ulcer therapy. Further work could elucidate the other mechanisms involved in the anti-ulcer effect of L-carnitine.

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