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ORIGINAL ARTICLE

Angiotensin antagonists and renal ischemia/reperfusion: Possible modulation by L-carnitine

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KEYWORDS

L-carnitine;
Ischemia/reperfusion;
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Oxidative stress;
Ramipril

Abstract *Introduction:* Ischemia/reperfusion (I/R) injury and therapy with angiotensin antagonists were shown to exert significant effects on the kidney. The study aimed to investigate the protective effect, if any, of L-carnitine on the initial nephrotoxic effects of ramipril or losartan on I/R insult in rats.
Methods: I/R was induced through bilateral renal ischemia for 60 min followed by 60 min of reperfusion. Groups I and II received both 1% Tween 80 p.o. and saline i.p. and served as sham-operated and I/R control groups, respectively. Groups III–VII received 2 weeks pretreatment with ramipril (1 mg/kg; p.o.), losartan (10 mg/kg; i.p.), L-carnitine (200 mg/kg; i.p.) and L-carnitine plus either ramipril or losartan, respectively. Chosen markers included kidney function tests, oxidative stress and inflammatory biomarkers as well as histological assessment of kidney sections.
Results: I/R increased plasma creatinine and urea levels but decreased albumin level; meanwhile, it increased the kidney tumor necrosis factor-alpha (TNF-α) content, myeloperoxidase (MPO) and plasma lactate dehydrogenase (LDH) activities. Moreover, I/R decreased kidney carnitine, glutathione, and total nitrate/nitrite contents as well as superoxide dismutase activity. Both ramipril and losartan elevated creatinine and urea levels; meanwhile, they lowered raised LDH, TNF-α and MPO as compared to I/R-control group. L-carnitine alone or combined with either agent decreased creatinine and urea levels, LDH and MPO activities as well as TNF-α content as compared to ramipril or losartan monotherapy.

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Conclusions: L-carnitine can protect the kidney from the initial deleterious effects of either ramipril or losartan in rats subjected to I/R most probably by virtue of its antioxidant and anti-inflammatory effects.

1. Introduction

Acute renal failure (ARF) resulting from ischemia/reperfusion (I/R) injury is a serious clinical problem. I/R injury in the kidney may occur during transplantation, shock or cardiovascular surgery.[1]

The activation of the renin angiotensin system (RAS) plays critical roles in the progression of chronic kidney disease, such as diabetic nephropathy.[2] Therefore, drugs that influence the RAS are used with increasing frequency in the treatment of chronic renal and vascular diseases. However, a well-known side effect of such drugs is acute worsening of renal function in certain patients, depending on the state of hydration and the kind of pre-existing renal damage, due to predominant dilatation of efferent arterioles and consequent decrease of glomerular filtration rate (GFR).[3,4]

The kidney plays an important role in carnitine homeostasis due to its ability to reabsorb 95% of carnitine in the glomerular filtrate. Impairment of this reabsorptive function due to renal injury can lead to systemic carnitine deficiency which may require supplementation with exogenous carnitine.[5]

The present study aimed to investigate the protective effect, if any, of L-carnitine on the initial nephrotoxic effects of angiotensin antagonists such as ramipril and losartan on I/R insult in rats. Chosen markers of nephrotoxicity included kidney function tests, oxidative stress and inflammatory biomarkers as well as histological assessment of kidney sections.

2. Material and methods

2.1. Material

2.1.1. Animals

Adult male albino rats, weighing 200–250 g, were used in the present study. They were obtained from the animal house of Faculty of Pharmacy, Cairo University where they were maintained under controlled environmental conditions and fed a standard chow diet (El-Nasr Co., Cairo, Egypt) and water ad libitum throughout the experimental period. The study was performed according to the guidelines stated by the ethics committee of Faculty of Pharmacy, Cairo University.

2.1.2. Drugs

L-carnitine was purchased from Sigma–Aldrich (St. Louis, MO, USA) and losartan was obtained from Unipharma for Pharmaceutical Industries (Egypt). Both drugs were dissolved in saline such that each 100 g animal received 0.1 ml of the prepared solution intraperitoneally. Ramipril was obtained from Pharonia Pharmaceuticals Company (Egypt) and suspended in 1% Tween 80 such that each 100 g animal received 1 ml of the prepared suspension orally.

2.1.3. Chemicals

Thiobarbituric acid, vanadium III chloride, Ellman's reagent, reduced glutathione (GSH), superoxide dismutase (SOD), 1,1-3,3-tetraethoxypropane and hexadecyltrimethyl ammonium bromide were obtained from Sigma–Aldrich (St. Louis, MO, USA). All other chemicals were of analytical grade.

2.2. Experimental design

Animals were randomly allocated into seven groups each consisting of 10 rats. Drugs were administered daily for 14 successive days. I/R was performed 1 h after the last dose. Groups I and II received both 1% Tween 80 p.o. and saline i.p. and served as sham-operated and I/R control groups, respectively. Groups III–V received ramipril (1 mg/kg/day; p.o.)[6], losartan (10 mg/kg/day; i.p.)[7] and L-carnitine (200 mg/kg/day; i.p.)[8], respectively. Groups VI and VII received L-carnitine with either ramipril or losartan.

2.3. Methods

2.3.1. Induction of I/R and sampling

On the 14th day, all rats (fasted overnight) were subjected to ischemia for 60 min followed by 60 min of reperfusion. This was done in all groups except the 1st one which was just subjected to sham operation.[9]

At the end of the experiment, blood samples were collected retro-orbitally in heparinized tubes. The plasma was separated by centrifugation at 3000 rpm for 15 min at 4 °C, then divided into several aliquots and stored at −20 °C until time of analysis. Kidneys were dissected out and used to prepare 10% homogenate in ice-cold isotonic saline. The prepared homogenate and plasma were used for estimation of the chosen biochemical parameters. Moreover, histological assessment of kidney sections from all groups was performed.[10]

2.3.2. Estimation of renal function tests

Assessment of plasma creatinine, urea and albumin levels was achieved using commercial kits from Stanbio (USA) and expressed as mg/dl.

2.3.3. Estimation of tissue damage biomarkers

Plasma lactate dehydrogenase (LDH) activity was assessed using commercial kits from Stanbio (USA) and expressed as U/L.

2.3.4. Estimation of oxidative stress biomarkers

Kidney content of GSH was determined according to the method described by Ahmed et al.[11] and expressed as μg/g wet tissue. Kidney SOD activity was determined according to the method described by Marklund and Marklund[12] and expressed as U/g wet tissue. Kidney total nitrate/nitrite

(NO_x) content was determined according to the method of Miranda et al.[13] and expressed as μmol/g wet tissue.

2.3.5. Estimation of inflammatory biomarkers

Tumor necrosis factor-alpha (TNF-α) was determined in the kidney using a rat TNF-α ELISA kit (Biosource International, USA) and expressed as pg/g wet tissue. Renal myeloperoxidase (MPO) activity was assessed according to the method described by Manktelow and Meyer[14] and expressed as U/g wet tissue.

2.3.6. Renal carnitine content

Carnitine concentration was determined in the kidney homogenate according to the method reported by Prieto et al.[15] and expressed as nmol/g wet tissue.

2.4. Statistical analysis

Data were presented as means ± SE. A comparison between different treatment groups was achieved by one way ANOVA followed by Tukey–Kramer multiple comparison test using SPSS software version 13. $p < 0.05$ was chosen as the criterion for significance.

3. Results

3.1. Renal function tests

I/R resulted in an increase in plasma levels of creatinine and urea to about 2- and 3-folds, respectively, as compared to sham-operated group; meanwhile, it significantly decreased the albumin level to about half its normal value (Table 1).

Pretreatment with either ramipril or losartan significantly increased the creatinine level by 17.24% and 115.56%, respectively; meanwhile, L-carnitine significantly decreased creatinine level by 38.55% as compared to I/R control group. Combination of L-carnitine with either ramipril or losartan significantly decreased creatinine level by 26.42% and 21.92%, respectively, as compared to I/R control group and significantly decreased creatinine level as compared to ramipril or losartan monotherapy, respectively (Table 1).

Pretreatment with losartan increased urea level by 24.69%; whereas, pretreatment with L-carnitine significantly decreased urea level by 28.60%, while its combination with losartan did not significantly decrease urea level as compared to I/R control group, but it significantly decreased urea level as compared to losartan monotherapy. On the other hand, pretreatment with ramipril did not significantly alter urea level while its combination with L-carnitine significantly decreased urea level by 18.70% as compared to I/R control group and significantly decreased urea level as compared to ramipril monotherapy (Table 1).

Pretreatment with L-carnitine significantly increased the albumin level by 27.09%; meanwhile, pretreatment with ramipril or losartan did not significantly alter the albumin level as compared to I/R control group. Combination of L-carnitine with either ramipril or losartan increased the albumin level by 24.13% and 30.52%, respectively, as compared to I/R control group and significantly increased albumin level as compared to ramipril or losartan monotherapy, respectively (Table 1).

3.2. Tissue damage biomarkers

I/R resulted in an increase in the plasma LDH activity to about 3-folds as compared to sham-operated group. Pretreatment with ramipril or L-carnitine significantly decreased plasma LDH activity by 36.12% and 16.67%, respectively; meanwhile pretreatment with losartan normalized plasma LDH activity. Combination of L-carnitine with either ramipril or losartan decreased plasma LDH activity by 42.98% and 22.76%, respectively, as compared to I/R control group and its combination with ramipril significantly decreased plasma LDH activity as compared to ramipril monotherapy (Fig. 1).

3.3. Oxidative stress biomarkers

I/R showed a significant decrease in the kidney GSH content and SOD activity to 46% and 56% of the normal value, respectively. Moreover, it resulted in a significant decrease in NO_x content to 25% of the normal value (Fig. 2).

Pretreatment with ramipril, L-carnitine or combination of both agents significantly increased GSH content by 80.63%, 47.65% and 156.70%, respectively, as compared to I/R control group, combination of both agents significantly increased GSH content as compared to ramipril monotherapy, while pretreatment with losartan or its combination with L-carnitine normalized GSH content (Fig. 2a).

Pretreatment with ramipril, losartan or L-carnitine significantly increased SOD activity by 43.74%, 46.81% and 23.92%, respectively, as compared to I/R control group. Similarly, a combination of L-carnitine with either ramipril or losartan significantly increased SOD activity by 53.11% and 67.50%, respectively, as compared to I/R control group (Fig. 2b).

Pretreatment with ramipril, losartan or L-carnitine significantly increased NO_x content by 208.95%, 217.52% and 168.34%, respectively, as compared to I/R control group. Similarly, a combination of L-carnitine with either ramipril or losartan significantly increased NO_x content by 157.28% and 178.90%, respectively, as compared to I/R control group (Fig. 2c).

3.4. Inflammatory biomarkers

I/R showed a significant increase in the kidney MPO activity and TNF-α content to about 3- and 2-folds, respectively, as compared to sham-operated group (Fig. 3).

Pretreatment with ramipril or losartan normalized the MPO activity; meanwhile, pretreatment with L-carnitine or its combination with either ramipril or losartan significantly decreased MPO activity by 32%, 53.90% and 46.71%, respectively, as compared to I/R control group (Fig. 3a).

Pretreatment with either ramipril or losartan or the combination of L-carnitine with either of the two drugs normalized TNF-α content; meanwhile, pretreatment with L-carnitine significantly decreased TNF-α content by 27.39% as compared to I/R control group (Fig. 3b).

3.5. Kidney carnitine content

I/R showed a significant decrease in the kidney carnitine content to about 40% of the normal value. Pretreatment with ramipril normalized the kidney carnitine content. Pretreatment

Table 1 Effect of two weeks daily pre-treatment with ramipril, losartan and L-carnitine alone or in combination on plasma levels of creatinine, urea and albumin in rats subjected to renal ischemia/reperfusion (I/R).

Treatments	Parameters		
	Creatinine (mg/dl)	Urea (mg/dl)	Albumin (mg/dl)
Sham-operated control (1% Tween 80; p.o. + saline i.p.)	0.65 ± 0.02	22.42 ± 0.80	3.09 ± 0.03
I/R control (1% Tween 80; p.o. + saline i.p.)	1.35 ± 0.04*	67.17 ± 1.94*	1.54 ± 0.05*
Ramipril (1 mg/kg/day; p.o.)	1.58 ± 0.03$^{*,@}$	63.41 ± 6.28*	1.80 ± 0.07*
Losartan (10 mg/kg/day; i.p.)	2.91 ± 0.09$^{*,@}$	83.75 ± 4.44$^{*,@}$	1.70 ± 0.09*
L-carnitine (200 mg/kg/day; i.p.)	0.83 ± 0.03$^{*,@}$	47.96 ± 2.59$^{*,@}$	1.96 ± 0.11$^{*,@}$
Ramipril + L-carnitine	0.99 ± 0.03$^{*,@,\#}$	54.61 ± 3.56$^{*,@,\#}$	1.91 ± 0.08$^{*,@,\#}$
Losartan + L-carnitine	1.05 ± 0.04$^{*,@,\phi}$	65.69 ± 7.28$^{*,\phi}$	2.01 ± 0.15$^{*,@,\phi}$

Animals were pre-treated daily for 14 successive days with the test agents and subjected to I/R on the 14th day.
Each value represents mean of 8–10 rats ± SE.
Statistical analysis was performed using one way ANOVA followed by Tukey–Kramer multiple comparisons test.
* Significantly different from sham-operated control group at $p < 0.05$.
$^{@}$ Significantly different from I/R control group at $p < 0.05$.
$^{\#}$ Significantly different from ramipril group at $p < 0.05$.
$^{\phi}$ Significantly different from losartan group at $p < 0.05$.

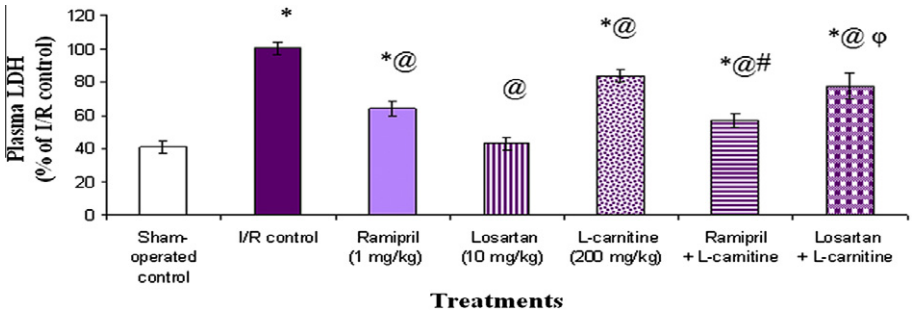

Figure 1 Effect of two weeks daily pre-treatment with ramipril, losartan and L-carnitine alone or in combination on plasma lactate dehydrogenase (LDH) activity in rats subjected to renal ischemia/reperfusion (I/R). Each bar with vertical line represents mean of 8–10 rats ± SE. Statistical analysis was performed using one way ANOVA followed by Tukey–Kramer multiple comparisons test. *Significantly different from sham-operated control group at $p < 0.05$. $^{@}$Significantly different from I/R control group at $p < 0.05$. $^{\#}$Significantly different from ramipril group at $p < 0.05$. $^{\varphi}$Significantly different from losartan group at $p < 0.05$.

with losartan, L-carnitine and the combination of L-carnitine with either ramipril or losartan significantly increased the kidney carnitine content by 244.67%, 262.03%, 288.98% and 325.51%, respectively, as compared to I/R control group. Combination of L-carnitine with either ramipril or losartan significantly increased the kidney carnitine content as compared to ramipril or losartan monotherapy, respectively (Fig. 4).

3.6. Histopathological examination of kidney sections

A section of a kidney of a sham-operated rat shows the normal architecture of renal tissue, being composed of a number of glomeruli embedded among a great number of different tubules which are the proximal and the distal convoluted tubules (Fig. 5a).

Induction of I/R resulted in a marked vacuolar degeneration in the lining epithelium of the tubules, interstitial edema and hemorrhage with cellular debris in the lumen of the tubules (Fig. 5b and c).

In the groups pretreated with ramipril or losartan before I/R, most of the tubules appeared normal in shape, except for a few ones that showed vacuolar degeneration in their lining epithelium and dilated blood capillaries (Fig. 6a and b).

Pretreatment with L-carnitine prevented I/R-induced degeneration in the tubular epithelium (Fig. 6c and d). Similarly, the combination of L-carnitine with either ramipril or losartan ameliorated most of the changes caused by either of the two drugs alone (Fig. 7a and b).

4. Discussion

In the present study, I/R resulted in marked glomerular and tubular dysfunction as evidenced by elevation of plasma creatinine and urea levels as well as reduction in albumin level. These results further support that reported previously by Sener et al.[16] Histopathological examination of I/R kidney sections showed marked vacuolar degeneration in the lining epithelium of the tubules, interstitial edema and hemorrhage with cellular debris in the lumen of the tubules.

The present elevation of LDH activity is considered as a marker of extensive necrosis consequent to I/R-induced oxidative stress leading to leakage of cellular contents as LDH.[17]

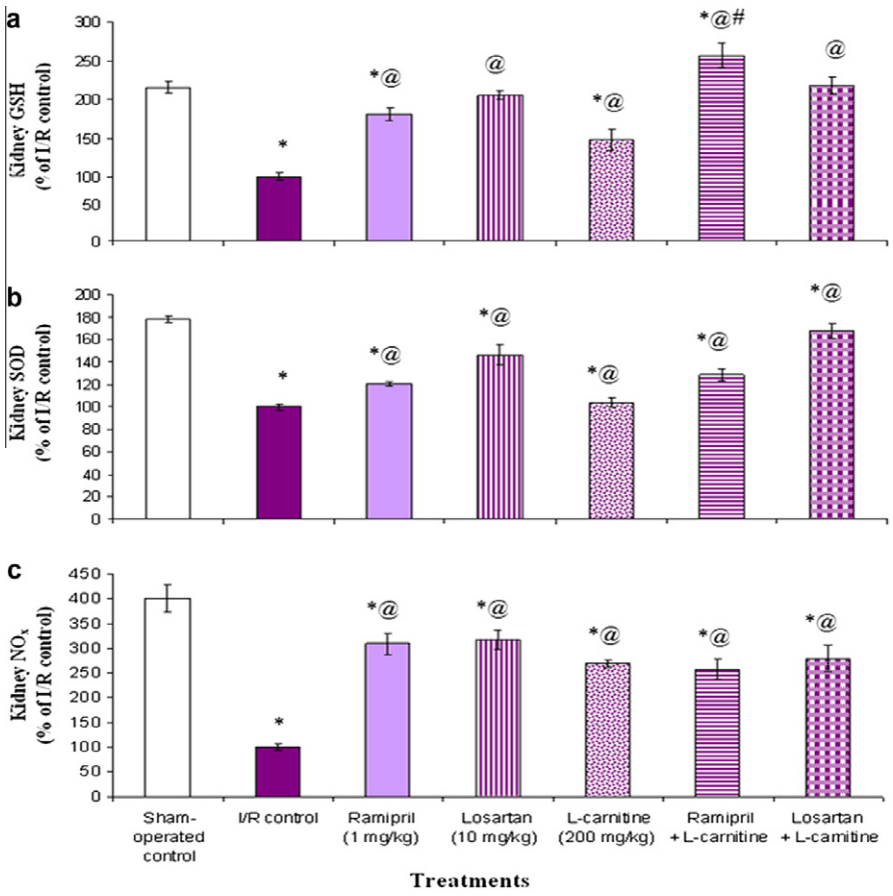

Figure 2 Effect of two weeks daily pre-treatment with ramipril, losartan and L-carnitine alone or in combination on kidney (a) glutathione (GSH) content, (b) superoxide dismutase (SOD) activity as well as (c) total nitrate/nitrite (NO_x) content in rats subjected to renal ischemia/reperfusion (I/R). Each bar with vertical line represents mean of 8–10 rats ± SE. Statistical analysis was performed using one way ANOVA followed by Tukey–Kramer multiple comparisons test. *Significantly different from sham-operated control group at $p < 0.05$. @Significantly different from I/R control group at $p < 0.05$. #Significantly different from ramipril group at $p < 0.05$. ϕSignificantly different from losartan group at $p < 0.05$.

The observed reduction in GSH content is probably due to its consumption during oxidative stress known to be associated by I/R.[18] A significant decrease in SOD activity was also observed which is in accordance to that reported by Feng et al.[19] Hypoxia, resulting from ischemia and subsequent reperfusion, is characterized by increased production of reactive oxidative species (ROS) and decreased efficacy of the antioxidant defenses as SOD.[20]

The observed interstitial edema, in histopathological sections, caused by I/R in the present study was supported by the elevation of inflammatory biomarkers such as renal TNF-α content and MPO activity. Similar results were previously reported.[18,21] Renal TNF-α contributes to neutrophil infiltration and early injury after I/R.[22]

Polymorphonuclear leukocytes accumulated during reperfusion have long been implicated as critical mediators of I/R injury. These cells are a potential source of ROS and have a major role in the development of oxidative tissue injury.[23] Similarly, the present increase in MPO activity in the kidney tissue following I/R is expected as MPO is primarily found in neutrophils and its activity reflects neutrophil infiltration in tissues.[24]

The observed decrease in NO_x content due to I/R injury is in accordance with that reported by Lieberthal et al.[25] who showed an impaired endothelium-dependent vascular relaxation in I/R. It is suggested that a reduced production of nitric oxide (NO) through impairment in its synthetic pathway is involved in renal failure.[26] NO plays a key role not only in the regulation of renal hemodynamics but also in renal tubular function.[27]

I/R-induced renal dysfunction could be also related to energy starvation as shown by a low carnitine content in I/R group. Similar results were obtained by Aleisa et al.[28] who reported that cisplatin-induced carnitine deficiency and ATP depletion could lead to renal dysfunction. I/R was proven to cause severe damage to renal proximal tubules[29] leading to impaired renal synthesis and inhibition of tubular reabsorption of carnitine.[30]

The present study showed that both ramipril and losartan administration augmented glomerular dysfunction induced by I/R on the kidney, where significant elevation in plasma creatinine and urea levels was observed. These results were further confirmed by the histopathological examination of kidney sections from these groups. Retention of creatinine and urea during therapy with angiotensin antagonists was reported by Demeilliers et al.[31] in one kidney, one clip Na^+ restricted rats and Helmchen et al.[32] in hypertensive rats with bilaterally

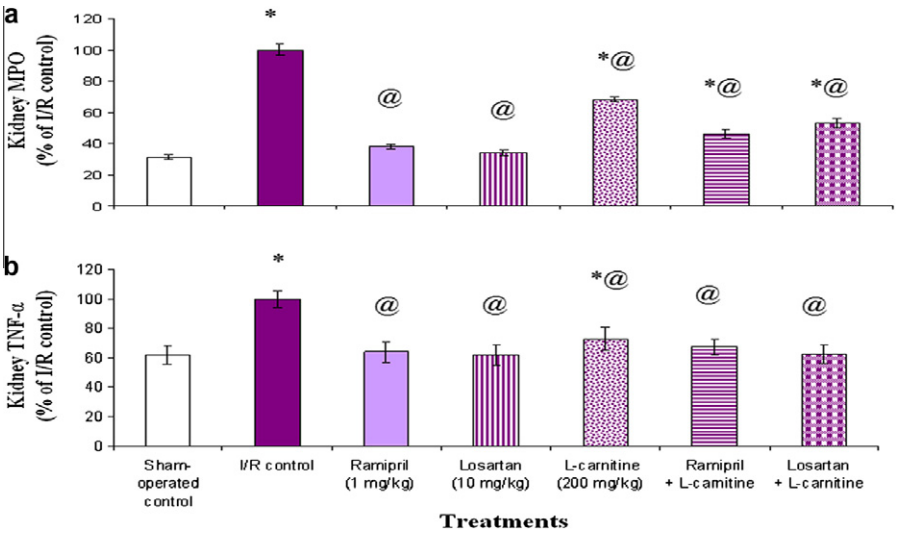

Figure 3 Effect of two weeks daily pre-treatment with ramipril, losartan and L-carnitine alone or in combination on kidney (a) myeloperoxidase (MPO) activity and (b) tumor necrosis factor-alpha (TNF-α) content in rats subjected to renal ischemia/reperfusion (I/R). Each bar with vertical line represents mean of 8–10 rats ± SE. Statistical analysis was performed using one way ANOVA followed by Tukey–Kramer multiple comparisons test. *Significantly different from sham-operated control group at $p < 0.05$. @Significantly different from I/R control group at $p < 0.05$.

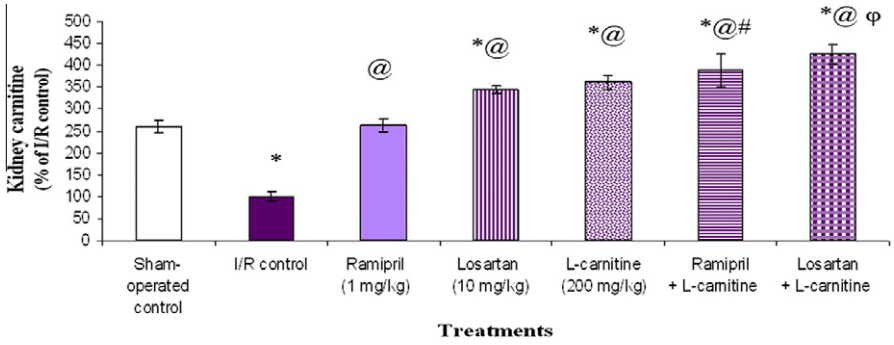

Figure 4 Effect of two weeks daily pre-treatment with ramipril, losartan and L-carnitine alone or in combination on kidney carnitine content in rats subjected to renal ischemia/reperfusion (I/R). Each bar with vertical line represents mean of 8–10 rats ± SE. Statistical analysis was performed using one way ANOVA followed by Tukey–Kramer multiple comparisons test. *Significantly different from sham-operated control group at $p < 0.05$. @Significantly different from I/R control group at $p < 0.05$. #Significantly different from ramipril group at $p < 0.05$. φSignificantly different from losartan group at $p < 0.05$.

constricted renal arteries. ARF complicating Ang II antagonists' therapy is almost caused by the loss of GFR resulting from an inadequate glomerular capillary pressure.[33]

Ang II has been considered to be involved through an Ang II type 1 receptor-NADPH oxidase pathway in the production of ROS by the mesangial and tubular cells,[34] hence preventing such actions by ACE inhibition or Ang II receptor blockade could explain the present decrease in oxidative stress biomarkers by ramipril and losartan pretreatment. This could also explain the observed reduction in LDH activity which reflects tissue injury consequent to oxidative stress.

In the current study, administration of ramipril or losartan normalized I/R-induced increase in MPO activity and TNF-α content. This was coupled by reduction in renal interstitial inflammation shown in the histopathological examination. The present data are in accordance with previous reports which demonstrated that ACE-inhibition prevents postischemic coronary leukocyte adhesion and leukocyte-dependent reperfusion injury.[35] Krámer et al.[36] also reported anti-inflammatory and antiaggregatory properties of losartan.

Pretreatment with ramipril or losartan in the present study was shown to increase the kidney NO_x content. Mechanisms that account for the effects of ACE inhibitors and ARBs on vascular dysfunction have been reported to be related to potentiating the actions of bradykinin in spontaneously hypertensive rats,[37] an increase in nitric oxide synthase (NOS) activity in aging rats,[38] and/or by inhibiting the influence of Ang II on oxidative stress[39] which subsequently leads to improving the biological half-life of NO.[40]

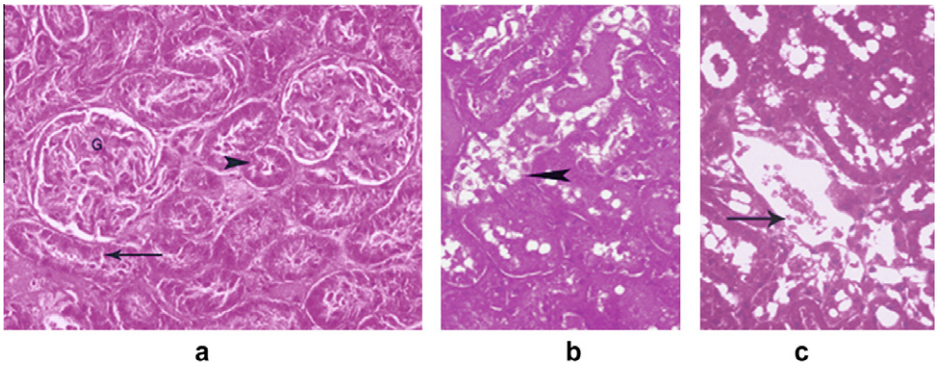

Figure 5 Sections of kidneys from (a) normal rat showing the normal architecture of renal tissue, being composed of a number of glomeruli (G) embedded among a great number of different tubules. The most prominent of these tubules were the proximal convoluted tubules (arrow head) lined with pyramidal cells and the distal convoluted tubules (arrow) with larger diameter and lined with cuboidal cells; (b and c) rats subjected to ischemia/reperfusion showing marked vacuolar degeneration in the lining epithelium of the tubules (arrow head) as well as interstitial edema and hemorrhage (arrow) with cellular debris in the lumen of the tubules (H and E × 200).

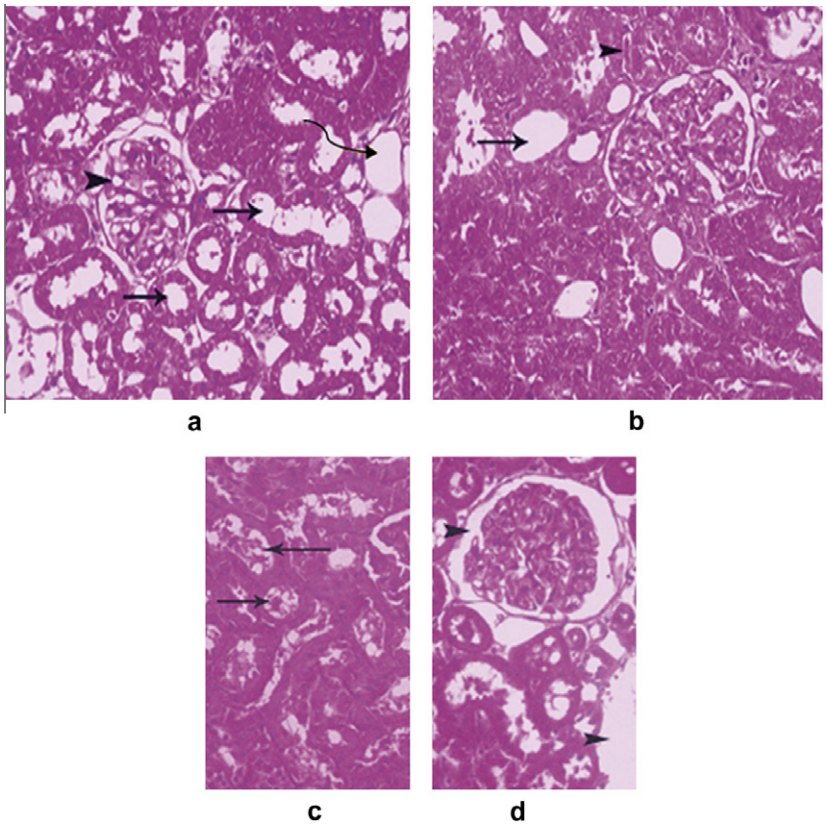

Figure 6 Sections of kidneys of rats subjected to ischemia/reperfusion-induced nephrotoxicity after treatment with (a) ramipril showing glomeruli with signs of vacuolar degeneration (arrow head) with most of the tubules appearing normal in shape (arrow), except for a few ones that show signs of vacuolar degeneration (arrow) in their lining epithelium. Blood capillaries (wavy arrow) appear more or less dilated denoting increased blood flow; (b) losartan showing dilated blood capillaries (arrow) and small areas of hemorrhage in between the tubules (arrow head) and (c and d) L-carnitine showing no signs of degeneration in the tubular epithelium, but cellular debris were still present in the lumen of the tubules (arrow) denoting a process of regeneration and increased urinary space in the renal corpuscle and in the interstitial tissue (arrow head) denoting increased urinary output (H and E × 200).

In the present study, pretreatment with L-carnitine improved I/R-induced kidney dysfunction as it decreased plasma creatinine and urea levels and increased albumin level. Histopathologically, sections from L-carnitine-treated group showed no signs of degeneration in the tubular epithelium. Propyl L-carnitine, an ester derivative of L-carnitine, has been found to be of value in preventing decline in renal function that occurs during I/R.[41]

Moreover, Ahmad et al.[42] reported that carnitine administration to patients undergoing hemodialysis in end-stage renal

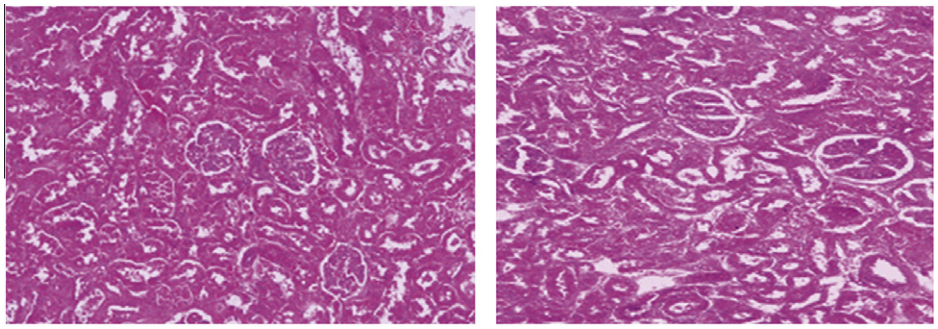

Figure 7 Sections of kidneys of rats subjected to ischemia/reperfusion-induced nephrotoxicity after treatment with (a) ramipril + L-carnitine showing little degeneration in some of the tubules and slight edema denoting reduction of the interstitial inflammation and (b) losartan + L-carnitine showing most of the tubules normal in shape, only some of them show degrees of vacuolar degeneration with little interstitial hemorrhage. (H and E × 100).

disease decreased protein catabolism and/or enhanced protein synthesis, thereby reducing serum concentrations of the products of protein catabolism, including urea, creatinine and phosphorus.

Pretreatment with L-carnitine significantly increased GSH content and SOD activity and decreased LDH activity. Chang et al.[43] reported that L-carnitine suppressed the release of free electrons from mitochondrial electron transport systems, a prerequisite reaction to the generation of ROS.

L-carnitine pretreatment completely reversed the I/R-induced decrease in carnitine content to control values. L-carnitine accumulates in the kidney and stimulates shuttling of long-chain fatty acids across the inner mitochondrial membrane for beta-oxidation in mitochondria, with a consequent increase in ATP production which could account for some of the favorable effects caused by L-carnitine.[44]

Pretreatment with L-carnitine in the present study also decreased kidney TNF-α content, MPO activity and increased NO_x content.

The study by Gorur et al.[45] reported that L-carnitine was associated with a decreased tissue inflammation and neutrophil infiltration in a rat kidney I/R injury model, which supports the findings of the present study.

Carnitine interacts with NO/cGMP system at least in part through its ability to increase both endothelial NOS gene and protein expressions. As a result, it is expected to provide protection from oxidative stress through increased bioavailability of NO which has also been shown to have antioxidant effects.[46]

The current study showed that the combined administration of L-carnitine with either ramipril or losartan decreased plasma levels of creatinine and urea and increased albumin level. Thus both agents could serve to reduce the deleterious effects of ACE inhibitors and ARBs in this perspective.

In the present investigation, combined administration of L-carnitine with either ramipril or losartan caused enhancement of renal GSH content as well as reduction of plasma LDH activity. The improvement produced by the latter combinations can be attributed to the previously discussed antioxidant activities reported for each of the used agents.[34,43]

Data of the present work revealed that pretreatment of rats with ramipril or losartan in combination with L-carnitine decreased inflammatory biomarkers and MPO activity owing to their documented anti-inflammatory properties.[35,36,45]

On the other hand, the apparent antagonism of losartan effects on plasma LDH activity when combined with L-carnitine may need further studies to investigate underlying mechanisms.

5. Conclusions

I/R exerted deleterious effects on kidney functions via enhancing the production of oxidative stress and inflammatory biomarkers as well as interference with energy stores. Both ramipril and losartan caused significant worsening in kidney function tests as evidenced by elevated creatinine and urea levels; meanwhile, they ameliorated oxidative stress and inflammatory biomarkers. L-carnitine protected against I/R-induced changes. Moreover, its combination with either ramipril or losartan attenuated some of their harmful effects on GFR. The favorable effects of L-carnitine are probably mediated by virtue of its antioxidant and anti-inflammatory effects or by a mechanism related to its ability to increase the intracellular carnitine content, with a consequent improvement in mitochondrial oxidative phosphorylation and energy production. This will open new perspectives for the use of L-carnitine in the treatment of renal diseases associated with or secondary to carnitine deficiency as acute renal insufficiency.

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