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Possible role of nitric oxide in hepatic injury secondary to renal ischemia-reperfusion (I/R) injury

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Abstract. Hepatic injury secondary to renal I/R injury has been documented in several studies. This study aimed to investigate the role of NO in hepatic injury secondary to renal I/R in rat model. Sprague-Dawley rats ($n = 48$) were divided into 4 equal groups; sham-operated, I/R injury group (45 min of bilateral renal ischemia), L-arginine group (I/R with 300 mg/kg L-arginine, 20 min before ischemia), L-NAME group (I/R with 50 mg/kg L-NAME, 20 min before ischemia). L-NAME (NO synthase inhibitor) caused significant elevation in serum creatinine, BUN, liver enzymes, liver histopathological damage score ($p \leq 0.05$) and MDA production ($p \leq 0.001$); on the other hand significantly decreased NO and GSH levels ($p \leq 0.05$). L-arginine significantly decreased serum creatinine, BUN and GSH ($p \leq 0.05$) and caused significant elevation in liver enzymes and NO ($p \leq 0.05$), and also in MDA levels ($p \leq 0.001$) in liver tissues. We conclude that endogenous NO might have protective effect against hepatic injury induced by renal I/R injury and inhibition of this endogenous NO by L-NAME or exogenous administration of NO (by L-arginine) might be harmful.

Key words: Renal — Ischemia — Reperfusion — Liver — Oxidative Stress — NO

Introduction

Renal ischemia-reperfusion (I/R) injury is an inevitable consequence of kidney transplantation and also results from systemic hypoperfusion with subsequent circulatory resuscitation and local renal hypoperfusion following partial nephrectomy and aortic cross-clamping (Weight et al. 2001). I/R injury is a complex phenomenon that induces cell damage through a bi-phasic process. Ischemia initiates the injury by deprivation of the energy needed to maintain ionic gradients and homeostasis, which may ultimately, leads to cellular dysfunction and death. Reperfusion exacerbates this damage triggering an inflammatory reaction in which participate oxygen free radicals, endothelial factors and leukocytes (Devarajan 2006). Reactive oxygen species (ROS) and nitric oxide (NO) play an important role in mediating cell damage during I/R injury (Noiri et al. 2001; Basireddy et al. 2006).

Liver and kidney are important regulators of body homeostasis and are involved in excreting the toxic products of metabolism and exogenous drugs (Sural et al. 2000). Recent studies have suggested cross-talk between the liver and kidneys and found that any injury to either of them may affect the other. Liver injury is one of the distant-organ damages induced by kidney I/R. It has been demonstrated that renal I/R injury causes a significant increase lipid peroxidation (Yildirim et al. 2003; Vaghasiya et al. 2010) and decrease in antioxidant enzyme activities in liver tissues (Serteser et al. 2002). Recently, Kadkhodaee et al. (2009) demonstrated significant decrease in liver GSH, as well as a significant increase in proinflammatory cytokines; TNF-α and IL-10 concentrations in liver after renal I/R injury.

NO is an important mediator of the physiological and pathological processes in renal I/R injury (Lopez-Neblina

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et al. 1994; Yu et al. 1994; Lopez-Marti et al. 2003). There remains continuing uncertainty about the role of NO in renal I/R injury with theoretical and experimental evidences offering support for both toxic and protective role. Some studies have reported that NO induces cellular cytotoxicity and tissue injury *via* lipid peroxidation, DNA damage, and proapoptotic effects, which are part of I/R injury (Chatterjee et al. 2003; Goligorsky et al. 2002). On the other hand, many studies have demonstrated that increased NOS activity is associated with reduced I/R injury and increased blood flow in the ischemic region (Thadhani et al. 1996). To the best of our knowledge, no study investigated the role of NO in pathogenesis of the hepatic injury secondary to renal I/R injury. So, the aim of this experimental study was to test if there is a role for NO in pathogenesis of hepatic injury secondary to renal I/R injury in Sprague-Dawley rats.

Materials and Methods

Experimental animals

This study was conducted on 48 adult male healthy Sprague Dawley rats weighing between 250–300 g aging 4–6 months. Animals were bred and housed in the animal house of the Medical Experimental Research Center (MERC), Mansoura University, at a temperature of 20°C, fed a standard laboratory chow and had a free access to tap water. The protocol was approved by our local ethics committee.

Experimental design

Rats were randomly allocated into 4 groups (12 rats each):

Group I (sham) – subjected to all experimental procedure without renal ischemia.

Group II (I/R) – subjected to all experimental procedure with bilateral 45 min renal ischemia plus with injection of 0.5 ml saline *via* penile vein 20 min before ischemia.

Group III (L-arginine) – I/R group with administration of L-arginine (NO precursor) 300 mg/kg/b.w. in 0.5 ml saline *via* penile vein 20 min before ischemia.

Group IV (L-NAME) – I/R group with administration of N-omega-nitro-L-arginine methyl ester (L-NAME; nitric oxide synthase (NOS) inhibitor) 50 mg/kg/b.w. in 0.5 ml saline *via* penile vein 20 min before ischemia.

Model of bilateral renal ischemia/reperfusion injury

The rats were obtained from cages, kept for 30 s in a glass container containing a piece of cotton soaked with 10 ml of halothane. Then animals were maintained on Na^+-thiopental at a dose of 12 mg/100 g b.w. injected intraperitoneally. After anesthesia, the animal was fixed in the supine position on a thermoregulated heating board to maintain body temperature at 37°C. Then a midline laparotomy was done, then both renal pedicles were exposed and were clamped for 45 min using a vascular Bulldog clamp. Then the vascular clamps were released and reperfusion was maintained for 2 hours.

Collection of blood samples and tissues

Two hours after release of vascular clamp, the animal was euthanized by high dose of Na^+-thiopental then a blood sample (1.5 ml) was collected from the heart. The blood sample was centrifuged then serum was stored at –20°C for the time of analysis of serum creatinine, blood urea nitrogen (BUN), and liver enzymes ALT and AST. Kidney and liver specimens were rapidly harvested and prepared for histopathological examination and assay of NO and oxidants and antioxidants.

Biochemical assay

Serum concentrations of creatinine, BUN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by commercially available kits (Fortress diagnostics, UK).

Histopathological study

After sacrifice the kidney and liver were rapidly harvested from the animal, then the kidney and part of the liver were placed in 10% formalin solution immediately, left overnight, and then embedded in paraffin blocks. The blocks were cut in 4 μm sections and stained with hematoxylin-eosin, using standard protocols for light microscopic examination. The sections were viewed and photographed using an Olympus light microscope (Olympus BX51, Tokyo, Japan) with an attached photographic machine (Olympus E–330, Olympus Optical Co. Ltd, Japan).

Histopathology for liver tissues was evaluated *per* section in at least 10 randomly selected non-overlapping fields at ×400 magnifications of the sections. All sections were evaluated for the degree of portal inflammation, vacuolar degeneration, fatty degeneration, and vascular congestion. Each liver slide was examined, and the severity of the changes observed was scored using a scale of none (0), mild (1), moderate (2), and severe (3) damage (Coskun et al. 2007).

Kidney damage score was evaluated in approximately one hundred tubules *per* section which were selected randomly at ×400 magnification, and scored according to the following criteria: 0, normal; 1, areas of tubular epithelial cell swelling, vacuolar degeneration, necrosis and desquamation involving <25% of the tubular profile; 2, similar changes involving >25% but <50% of the tubular profile; 3, similar changes involving >50% but <75% of the tubular profile; 4, similar changes involving >75% of the tubular profile according to Miyaji et al. (2001).

Estimation of malondialdehyde (MDA), catalase and reduced glutathione (GSH) in liver tissues

The second part of liver was kept in cold conditions (precooled in Petri dish inverted on ice). It was cross-chopped with surgical scalpel into fine slices in chilled 0.25 M sucrose and quickly blotted on a filter paper. The tissue was minced and homogenized in 10 mM Tris-HCl buffer, pH 7.4 (10% w/v), with 25 strokes of tight Teflon pestle of glass homogenizer at a speed of 2500 rpm. The clear supernatant was used for assays of the marker of lipid peroxidation, malondialdehyde (MDA), catalase (CAT) enzyme, and reduced glutathione (GSH) by commercially available kits (Biodiagnostic Company, Dokki, Giza, Egypt).

Determination of nitric oxide level

Nitrite (metabolite of NO) in liver homogenate was measured according to the manufactural instructions (Biodiagnostic, Egypt, catalog #NO 2532). Briefly, in acidic medium, nitrite forms bright reddish-purple azo dye with sulphanilamide and N-(1-naphthyl) ethylenediamine. The colour of the dye can be measured at 540 nm and the final concentration of NO was measured in μmol/g liver tissue.

Statistical analysis

The results were expressed as mean ± SD. One away ANOVA test with Tukey's posthoc test was used to find statistical difference among various groups. The null hypothesis was rejected at the 0.05 level of significance. SPSS 16.0 software was used for data analysis.

Results

Serum creatinine and BUN and liver enzymes (ALT and AST)

Compared to sham group, serum creatinine and BUN were significantly high in I/R, L-arginine and L-NAME groups ($p < 0.05$). Also, serum creatinine and BUN showed significant decrease in L-arginine group and increase in L-NAME group compared to I/R group ($p < 0.05$). Moreover, these parameters were significantly increased in L-NAME group compared to L-arginine group. On the other hand, all groups showed significant elevation in serum levels of liver enzymes; ALT and AST in comparison with those of sham group ($p < 0.05$). Also, serum levels of ALT and AST were significantly high in L-arginine and L-NAME group compared to I/R group. Moreover, ALT and AST were significantly high in L-NAME group compared with L-arginine (Table 1).

Kidney and liver histopathological examination

Tables 2 and 3 and Figures 1and 2 show the results of kidney and liver damage score. Compared to sham group, the kidney weight was significantly high in I/R and L-NAME groups, 2 h after reperfusion ($p < 0.05$) (Table 2). Sham group showed normal kidney with preserved glomerular and tubular structures (Fig. 1A). On the other hand, I/R group showed significant increase in histopathological damage score compared to sham group ($p < 0.05$) (Table 2). Kidney specimens obtained from rats of I/R showed congestion, tubular vacuolization and dilatation, luminal casts and debris and loss of brush border were significantly high I/R groups (Fig. 1B). Compared to I/R group, histopathological damage score showed significant attenuation in L-arginine group and significant worsening in L-NAME group ($p < 0.05$) (Table 2). Figure 1B is a representive sample of L-arginine group, while Fig. 1D is a representive sample of L-NAME group.

Compared to sham group, the weight of liver was significantly high in control I/R and L-NAME groups, 2 h after reperfusion ($p < 0.05$) (Table 3). Sham group livers showed normal architecture with preserved structure of hepatic lobules (Fig. 2A). Also, histopathological examination of liver tissues from I/R showed normal liver architecture except liver vacuolization in few hepatocytes and leucocyte infiltration (Fig. 2B). However, fatty degenerative changes, vacuolization and leucocyte infiltration were significantly high in L-arginine group compared to I/R group (Table 3 and Fig. 2C). Also, compared

Table 1. Effects of renal ischemia on serum creatinine, BUN and liver enzymes (ALT and AST)

Group	Serum creatinine (mg/dl)	Serum BUN (mg/dl)	ALT (IU/ml)	AST (IU/ml)
Sham	0.475 ± 0.069	48.50 ± 5.63	139.75 ± 16.25	318.75 ± 89.53
I/R	0.667 ± 0.13*	82.15 ± 12.39*	146.00 ± 65.61*	352.25 ± 144.35*
L-arginine	0.577 ± 0.028	57.600 ± 14.69*#	221.00 ± 49.92*#	543.00 ± 111.13*#
L-NAME	0.79 ± 0.033*#$	94.63 ± 5.37*#$	395.00 ± 80.44*#$	797.00 ± 153.01*#$

All data expressed as mean ± SD. One way ANOVA with Tukey's *post hoc* test. BUN, blood urea nitrogen; I/R, ischemia/reperfusion; ALT, alanine transaminase; AST, aspartate transaminase. * $p < 0.05$ *vs.* sham group, # $p < 0.05$ *vs.* I/R group, $ $p < 0.05$ *vs.* L-arginine group.

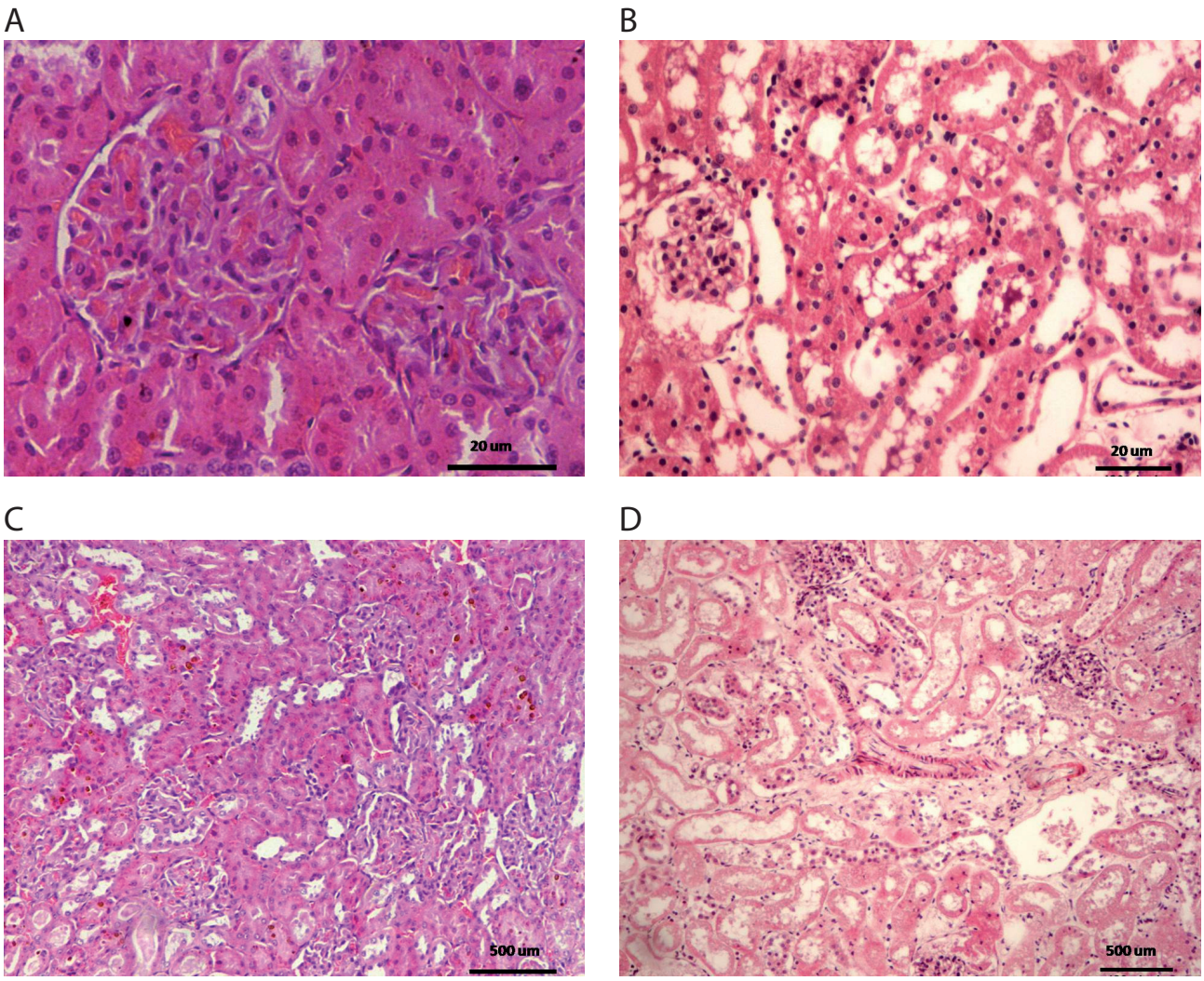

Figure 1. Kidney specimens showing (**A**) normal kidney cortical area with preserved glomerular structure and proximal convoluted tubules with mild degeneration (sham group) (magnification ×400, H&E); (**B**) tubular dilatation, vacuolization, and necrosis and atrophied glomeruli with dilatation of Bowman space (I/R group) (×400, H&E); (**C**) nearly normal kidney structure with mild interstitial haemorrhage and intraluminal casts (L-arginine group) (×200, H&E); (**D**) cystic dilatation of renal tubules, vacuolization, necrosis with loss of luminal borders of tubular epithelial cells with inflammatory interstitial infiltrate L- NAME group (×400, H&E). H&E, haematoxylin and eosin.

Table 2. Histopathological damage score of kidney tissues in different groups

Group	Kidney weight (g/100 g b.w.)	Congestion	Tubular vacuolization and dilatation	Luminal debris and casts	Loss of proximal tubules brush borders
Sham	0.42 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
I/R	0.65 ± 0.01*	1.00 ± 0.00*	0.88 ± 0.11*	1.00 ± 0.00*	1.00 ± 0.00*
L-arginine	0.47 ± 0.11$^{\#}$	0.41 ± 0.16$^{*\#}$	0.14 ± 0.02$^{*\#}$	0.33 ± 0.26$^{*\#}$	0.41 ± 0.03$^{*\#}$
L-NAME	0.94 ± 0.08$^{*\#\$}$	1.16 ± 0.12$^{*\#\$}$	1.20 ± 0.01$^{*\#\$}$	1.69 ± 0.16$^{*\#\$}$	1.26 ± 0.14$^{*\#\$}$

All data expressed as mean ± SD. One way ANOVA with Tukey's *post hoc* test was used. I/R, ischemia/reperfusion. * $p < 0.05$ *vs.* sham group, $^{\#}$ $p < 0.05$ *vs.* I/R group, $^{\$}$ $p < 0.05$ *vs.* L-arginine group.

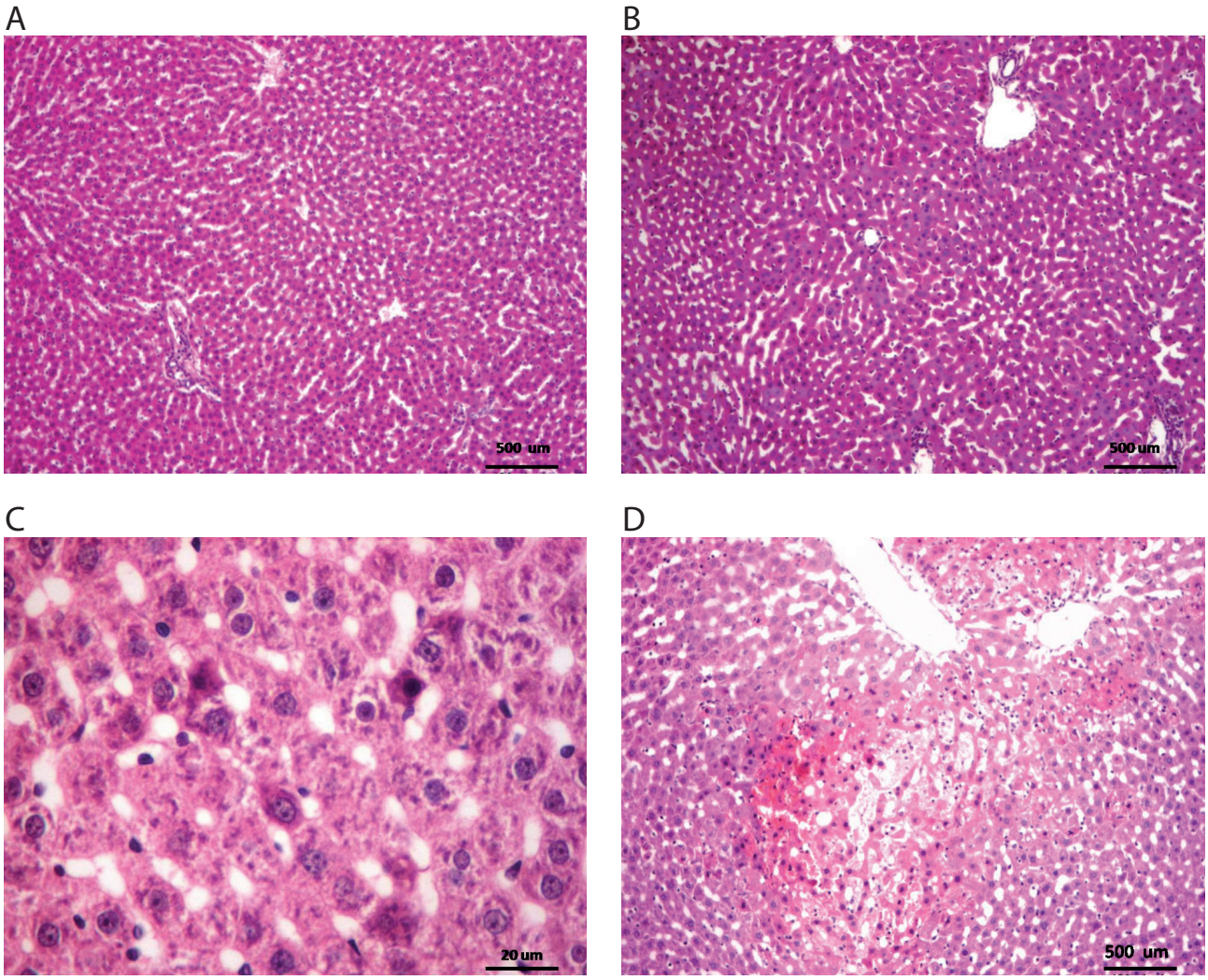

Figure 2. Specimens of liver tissues. **A.** Normal liver with the characteristic pattern of the hepatocytes trabeculae between central veins and portal areas (sham group) (×200, H&E). **B.** Nearly normal liver with the characteristic pattern of the hepatocytes trabeculae between central veins and portal areas with few inflammatory cell infiltrate (I/R group) (×200, H&E). **C.** Vacuolization and focal degenerative changes and many hepatocytes start to lose their nuclei by fragmentation and disappearance (L-arginine group) (×400, H&E). **D.** Vacuolization, and focal degenerative changes mainly in zone 3 with areas of haemorrhage and some inflammatory cells and some spaces start to appear in this zone 3 and in the lumen of the central vein (L-NAME group) (×200, H&E). H&E, haematoxylin and eosin.

Table 3. Histopathological damage score of liver tissues in different groups

Group	Liver weight (g/100 g b.w.)	Congestion	Vacuolization	Fatty degenerative changes	Leucocyte infiltration
Sham	3.29 ± 0.52	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
I/R	4.97 ± 0.91*	0.00 ± 0.00	0.143 ± 0.04*	0.00 ± 0.00	0.143 ± 0.04*
L-arginine	5.01 ± 0.03$^{\#}$	0.16 ± 0.01$^{*\#}$	0.16 ± 0.01*	0.16 ± 0.01$^{*\#}$	0.16 ± 0.01$^{*\#}$
L-NAME	7.21 ± 1.04$^{*\#\$}$	0.32 ± 0.02$^{*\#\$}$	1.00 ± 0.00$^{*\#\$}$	1.00 ± 0.00$^{*\#\$}$	1.16 ± 0.14$^{*\#\$}$

All data expressed as mean ± SD. One way ANOVA with Tukey's *post hoc* test was used. I/R, ischemia/reperfusion. * $p < 0.05$ *vs.* sham group, $^{\#}$ $p < 0.05$ *vs.* I/R group, $^{\$}$ $p < 0.05$ *vs.* L-arginine group.

to I/R group the liver damage score was significantly high in L-NAME group compared to control ischemic and L-arginine group (Table 3 and Fig. 2D).

Nitric oxide (NO), lipid peroxidation (MDA), and antioxidant (GSH, catalase) markers in liver tissues

The concentration of NO was significantly high in liver tissues of I/R group compared to sham group ($p < 0.05$). Compared to I/R group, NO concentration was significantly low in L-NAME group and significantly high in L-arginine group ($p < 0.05$) (Fig. 3A).

Compared to sham group, MDA was significantly high in liver tissues of all studied groups ($p \leq 0.001$). Compared to I/R group, MDA was significantly high in L-arginine group and L-NAME groups and it was significantly high in L-NAME group compared to L-arginine ($p = 0.000$) (Fig. 3B).

Compared to sham group, GSH and catalase were significantly low in liver tissues of all studied groups ($p \leq 0.01$). Compared to I/R group, GSH was significantly low in L-arginine and L-NAME groups ($p = 0.000$), but catalase in L-NAME and L-arginine groups showed no significant difference with I/R group (Fig. 3C,D).

Discussion

Renal I/R injury is a common clinical problem that encountered in many conditions such as transplantation, partial nephrectomy, sepsis, hydronephrosis, or elective urological operations. Although, most research studies in this area has

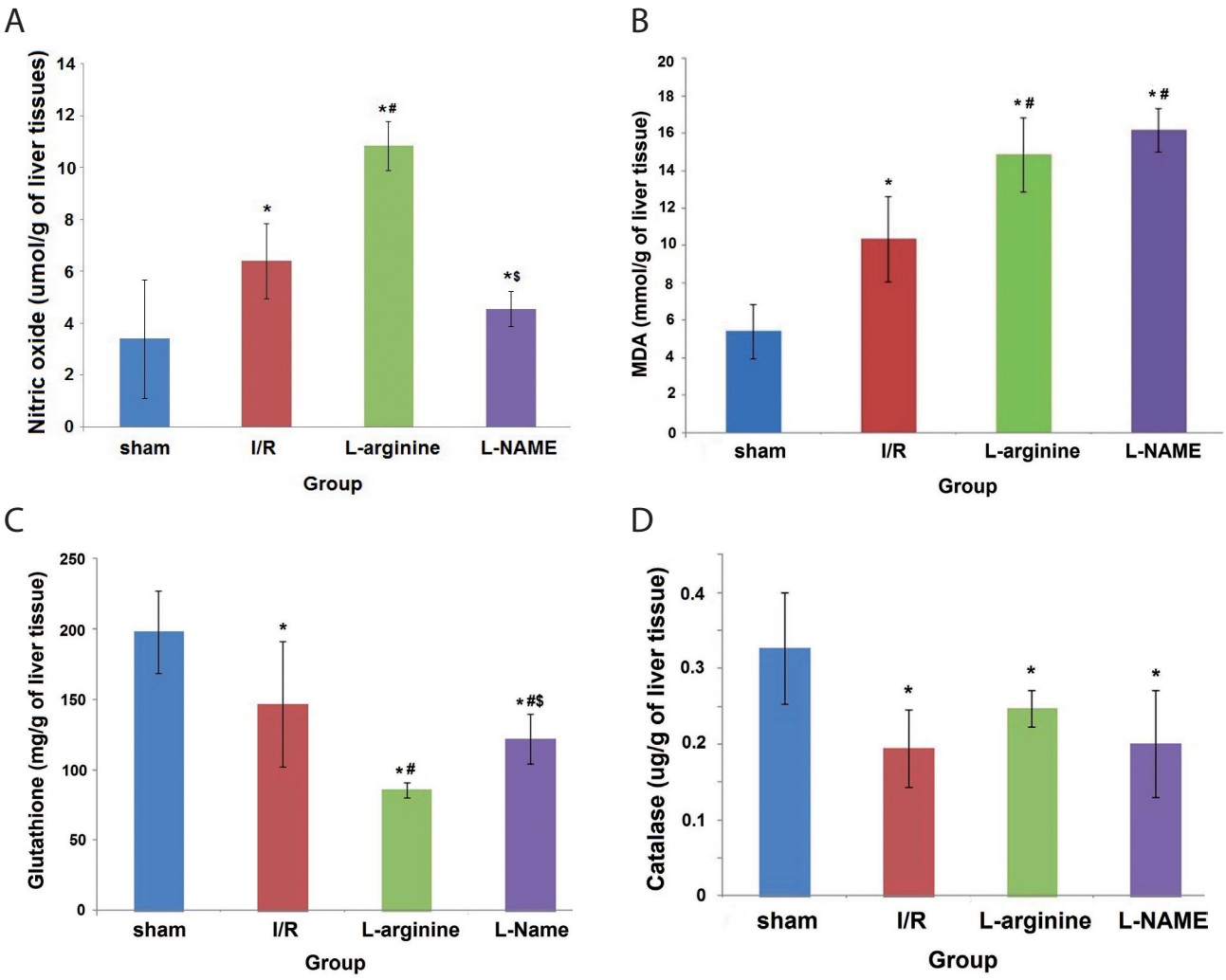

Figure 3. Oxidative stress markers in liver tissues from sham, I/R, L-arginine and L-NAME groups: concentration of NO (**A**), MDA (**B**), reduced glutathione (**C**) and catalase enzyme (**D**). * $p < 0.05$ *vs.* sham group, $^{\#}$ $p < 0.05$ *vs.* I/R group, $^{\$}$ $p < 0.05$ *vs.* L-arginine group.

focused on the local renal response to this injury (Kadkhodaee et al. 1996; Hussein et al. 2011), recent studies emerge to investigate the remote effects of renal I/R injury on distant organs such as liver, brain and lungs (Kelly 2003). In the present study, we investigated the role of NO in pathogenesis of hepatic injury secondary to renal I/R injury. The present study demonstrated, for the first time, that exogenous administration of either L-arginine (precursor of NO) or L-NAME (NOS inhibitor) that inhibit NO formation caused worsening of liver enzymes and liver morphology in a case of renal ischemia. Moreover, L-NAME effect was marked than L-arginine. These findings suggest that the endogenous NO might has a protective effect against hepatic injury induced by renal I/R injury and inhibition of this NO worsen the hepatic injury and unfortunately exogenous NO also worsen this hepatic injury.

In the present study, 45 min bilateral renal ischemia caused damage in kidney functions and morphology as evidenced by significant elevation in serum creatinine, BUN and histopathological damage score in I/R group compared to sham group, 2 h after reperfusion. These findings are in agreement with that demonstrated by Mahmoud et al. (2007) and Hussein et al. (2011). These studies shown deteriorations in kidney functions and kidney morphology by renal I/R injury. On the other hand, administration of L-arginine improved both renal functions and morphology, while administration of L-NAME caused more worsening in renal functions and kidney histopathological damage score. Previous studies demonstrated similar effects for L-arginine and L-NAME on kidney functions and morphology in rat models of 45 unilateral left renal ischemia with contralateral right nephrectomy (Rhoden et al. 2002; Mahmoud et al. 2007). The beneficial effect of the NO precursor L-arginine on the course of I/R injury provides an evidence for the functional NO deficiency. Decreased NO production in the course of ischemic acute renal failure has been described in a variety of experimental models (Yaqoob et al. 1996; Schramm et al. 2002). So, exogenous NO supply (by NO precursors such as L-arginine) could provide a protective effect on renal functions and morphology.

Enzymes ALT and AST are present in large quantities in liver cells or hepatocytes. Damage of hepatocytes by toxic or ischemic causes liberation of these enzymes in large amount from the damaged hepatocytes in blood and elevation of their blood concentration (Davidshon and Henary 1974; Sherlock et al. 1975). So they, specifically ALT, are good markers for hepatocyte damage by ischemic injury. In the present study significant elevation of these enzymes (ALT and AST) in I/R group compared to sham group was observed 2 h after reperfusion. This marked elevation in serum levels of liver enzymes was associated with little changes in hepatic morphology just few inflammatory cells infiltrate and hepatocyte vacuolization. The minimal changes in liver morphology might be due to sacrifice of rat at early time i.e. no time for morphological changes. In consistence with these findings previous studies demonstrated renal I/R injury caused hepatic injury (Kadkhodaee et al. 2009; Wang et al. 2010). Wang et al. (2010) in 60 min unilateral ischemia model demonstrated significant elevation in liver enzymes; ALT and AST and damage score of liver histology 1, 4, and 8 h post-reperfusion and the significant change was at 4 h after reperfusion. Also, they demonstrated significant elevation of MPO enzymes in early hours of reperfusion with the maximal elevation at 1 h of reperfusion and suggested early migration and activation of neutrophils and in liver tissues. Moreover, they observed mononuclear cell infiltration especially neutrophil infiltration in the liver central zone after renal I/R injury (Wang et al. 2010). On the other hand, Kadkhodaee et al. (2009) investigated the effect of different periods (30, 45 and 60 min) of bilateral renal ischemia on liver functions and histology. They concluded that minimum 45 min ischemia/60 min reperfusion is needed to study the effect of renal ischemia on liver functions and histology. That is why in our study we choose the model of bilateral renal ischemia for 45 min and 2 h reperfusion. Our results demonstrate impairment of liver functions and histology by renal ischemia for 45 min and reperfusion for 2 h. However, Serteser et al. (2002) concluded that 30 min renal ischemia, 60 min reperfusion is sufficient to elicit hepatic injury. This might be explained by difference in animal species used in each study. The present study and that of Kadkhodaee et al. (2009) used rat model but Serteser et al. (2002) used a mice model.

The potentially protective role of endogenous NO in tissues protection against I/R injury by ischemic postconditioning was suggested in many studies and there are several evidences implicating involvement of NO in the heart (Yang et al. 2004), kidney (Liu et al. 2007) and liver (Guo et al. 2011) protections by ischemic postconditioning. So, the main objective of this work was to investigate the role of endogenous and exogenous NO in pathogenesis of hepatic injury induced by renal I/R injury. The present study showed that inhibition of NOS by L-NAME (50 mg/kg b.w. 20 min before ischemia) caused more deteriorations in liver functions and histology. Unfortunately, NO precursor L-arginine (300 mg/kg b.w. 20 min before ischemia) caused also more worsening of liver functions and histology. Also, the concentration of NO in liver tissues was significantly high in I/R group compared to sham group. This elevation was significantly attenuated in L-NAME group and enhanced in L-arginine group. These findings indicate release of NO in liver tissues during renal I/R injury and this release enhanced by exogenous NO precursor (L-arginine) and blocked by NOS inhibitor (L-NAME). However, the source of this NO whether from endothelial NOS (eNOS) or inducible NOS (iNOS) was not investigated and this is one of the limitations of this study.

It has been reported that NO production by eNOS seems to be of central importance in ischemic injury (Jones et al. 2004) and eNOS-derived NO production constitutes a promising therapeutic approach to prevent myocardial I/R injury (Frantz et al. 2009). The L-NAME is non-selective inhibitor for NOS. So, further studies are recommended to investigate this point. However, the findings of the present study suggested that endogenous production of NO might be one of endogenous adaptive mechanisms that are triggered in liver to partially protect it against injury secondary to renal I/R injury. Inhibition of this production by L-NAME worsens the liver injury secondary to renal I/R injury. Moreover, enhancement of this production by exogenous NO precursors e.g. L-arginine also cause worsening of the hepatic injury secondary to renal I/R injury.

It is believed that I/R injury induces inflammatory response, which elicits tissue damage in a number of organs in which reactive oxygen (ROS) and nitrogen species play a key role in the pathophysiology of renal IR injury (Melin et al. 1997; Erdogan et al. 2006). The present study demonstrated significant increase in lipid peroxidation products malondialdehyde (MDA) and reduction in GSH and catalase enzyme activity in liver tissues. The findings indicate enhanced redox state in liver tissues during renal I/R injury. These findings are in agreement with Yildirim et al.(2003); Vaghasiya et al. (2010) who demonstrated significant increase lipid peroxidation secondary to renal I/R injury. Also, Serteser et al. (2002) demonstrated significant decrease in antioxidant enzyme activities in liver while Kadkhodaee et al. (2009) demonstrated significant decrease in liver GSH secondary to renal I/R injury. So, the question here, does ROS has a role in this action of NO or not? We found in the present study significant elevation in MDA (marker of lipid peroxidation) in both L-arginine and L-NAME groups; however, the elevation was significantly high in L-NAME. On the other hand, GSH was significantly low in both L-arginine and L-NAME groups compared to I/R group. But, catalase showed non-significant change in both L-arginine and L-NAME groups. So, these findings suggest that inhibition of ROS by endogenous NO might play a role in hepatic protection against renal I/R injury. However, the source of these ROS, whether liver of kidney this was not investigated in this study and further studies need to clarify this point.

Conclusion

This study confirmed hepatic injury secondary to renal I/R injury especially at the level of liver functions. Inhibition of endogenous NO by L-NAME caused deteriorations of liver functions and morphology. Unfortunately, exogenous NO (by L-arginine) worsened hepatic injury secondary to renal I/R injury. So, we concluded that endogenous not exogenous NO may have a protective effect on liver against renal I/R injury. This hepatoprotective effect of endogenous NO might be probably due to inhibition of formation of reactive oxygen species.

No conflicts of interest is declared by the author(s).

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