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Original Article

Beneficial Effects of Urapidil against Renal Ischemia Reperfusion-Related Renal Injury

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ABSTRACT

Objective: The potential protective effects of urapidil (Ura) against renal injury composed by ischemia reperfusion (I/R) were examined.

Methods: The experimental animals were assigned to sham, I/R, I/R + Ura 0.5 mg/kg, and I/R + Ura 5 mg/kg groups. Total antioxidant status (TAS), superoxide dismutase (SOD), total oxidant status (TOS), myeloperoxidase (MPO), oxidative stress index (OSI), and malondialdehyde (MDA) parameters were determined.

Results: MDA, TOS, MPO, and OSI values elevated, but TAS and SOD levels declined in the I/R group. Ura treatment reversed these parameters. In addition, immunopositivity of interleukin-1 beta and tumor necrosis factor-alpha were severe in the I/R group but declined due to Ura administration.

Conclusion: The results of the study showed that Ura is highly effective against renal damage induced by I/R.

INTRODUCTION

Following the ischemic phase, regaining of blood flow in tissues is called ischemia reperfusion (I/R).[1] When the blood flow of the kidney is partially or completely blocked due to any reason, tissues are damaged and kidney I/R injury occurs.[2] The kidney is quite susceptible to I/R injury related to renal structure.[3] Various surgical interventions lead to renal I/R injury such as renal transplantation, heart surgery, and partial nephrectomy.[4,5] Acute kidney injury (AKI) significantly increases the risks for morbidity and mortality[6] and mainly results from renal I/R.[7]

Oxidative stress is a result of derangement between oxidant and antioxidant systems. Enhanced reactive oxygen species (ROS) generation and diminished ROS removing ability are observed during oxidative stress.[8] Following the renal ischemia, ROS formation rate increases, which complicates reperfusion injury through lipid peroxidation and oxidative damage.[4] Malondialdehyde (MDA) demonstrates free radical activity and superoxide dismutase (SOD) is an indicator of ROS removing ability.[9] Increased ROS production is the primary element for the reperfusion injury.[10] Low antioxidant system activity including low SOD levels may be responsible for renal I/R injury.[11] Inflammatory cytokines play role in I/R-related neuronal injury.[12]

Linas et al.[13] mentioned that renal I/R injury was aggravated through active neutrophils. Neutrophil activation is associated with myeloperoxidase (MPO). Proinflammatory cytokines and ROS generation are connected with activated neutrophils.[14] Up to today, there has been no efficient therapy against renal I/R injury due to insufficient information about its pathophysiology.[15,16]

Several herbal-based and pharmacological agents have been examined to avoid oxidant damage.[17–20] Urapidil

(Ura) is a peripheral postsynaptic alpha 1-adrenoceptor antagonist, a well-tolerated agent in the management of blood pressure.[21] It enhances the tissue oxygen capacity and demonstrates antioxidant features.[22,23] However, the role of Ura injury has not been investigated yet against renal I/R. Here, we planned to find out how Ura acts against kidney damage at different doses in renal I/R.

MATERIALS AND METHODS

Chemicals

Ura (Urapidil, Sigma Aldrich Company) was prepared by dissolving in dimethyl sulfoxide (DMSO, Sigma Aldrich) and administered as intraperitoneal (i.p.) at low (0.5 mg/kg) and high (5 mg/kg) doses.[24–26] For anesthesia, we used 10 mg/kg, i.p. xylazine hydrochloride (Rompun, Bayer, Istanbul) and 60 mg/kg, i.p. ketamine (Ketas, Pfizer, Istanbul).

Ethical approval and animals

The current study was approved by our University Experimental Animal Ethics Committee (protocol number: 30.03.2018/58) and carried out at our University Experimental Animals Research and Application Center. Sprague–Dawley male rats were obtained from the same center. They were held under standard laboratory conditions such as appropriate light and dark cycle, humidity, and temperature and housed in polypropylene cages. Rats were fed with standard rat feed and were provided with drinking water. All animals were deprived of food 12 h before the experiment but were allowed to drink water.

Groups and I/R model

Surgical processes were applied to the back regions of the rats. Before surgical interventions, the animals were immobilized in face-down positioning and the back regions were shaved and disinfected with 10% povidone-iodine. Anesthesia was applied to animals.

A total of 32 Sprague–Dawley male rats, weighing 250–270 g, were randomly assigned to four groups. Group I (sham): the rats were incised and sutured via 3/0 silk suture without any intervention. Group II (I/R): followed the same procedures as group I, and renal I/R model was created as described in previous studies.[27] Bilateral renal veins and arteria were fixed with microvascular clamps for 1 h. Then, blood flow was recovered for 24 h by releasing the clamps during the reperfusion phase. In group III (low-dose Ura: I/R + Ura 0.5 mg/kg) and group IV (high-dose Ura: I/R + Ura 5 mg/kg), Ura was given to rats i.p. 30 min before reperfusion, at the doses of 0.5 mg/kg and 5 mg/kg, respectively, and I/R model was created.

Collection and storage of tissue specimens after sacrification

After the experiment, we sacrificed the rats under anesthesia by decapitation. The sacrificing process was performed following the 24 h of reperfusion. The renal tissues were excised and split into two pieces. One piece was held in a 10% formaldehyde solution, and the other piece was kept at −80°C for biochemical analyses.

Homogenization of the tissue samples and biochemical parameter determination

A 10% homogenate was prepared by adding phosphate buffer solution to kidney tissue samples and centrifuging them for 2 min at 12 000 rpm. A second centrifuge was performed to obtain supernatant. Interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) levels were gauged via ELISA kits (Elabscience, Wuhan, China). MDA level was measured due to the method presented by Ohkawa et al.[28] SOD activity was determined via protocol detected by Sun et al.[29] MPO activity was measured using a method improved by Bradley et al.[30] Total oxidant status (TOS) and total antioxidant status (TAS) evaluation was performed using appropriate kits (Rel Assay Diagnostics). The ratio of TOS to TAS was admitted as the oxidative stress index (OSI).

Immunohistochemical (IHC) staining

Kidney tissues were fixed in 10% formaldehyde solution for 24 h. Then, formaldehyde was removed by washing with tap water. Tissues were routinely dehydrated, cleared in two changes of xylene, and embedded in paraffin wax. After deparaffinized by xylene and rehydrated in graded alcohols, sections were incubated for 10 min in 0.3% H_2O_2 to quench the activity of endogenous peroxidase. Sections were heated to reveal antigens in the tissue in an antigen retrieval solution for 10 min. To minimize nonspecific bindings, a protein block solution was used. TNF-α (Novus Biological, Cat. No: NBP1-19532, Dilution: 1/100) and IL-1β (Bioss, Cat. No: bs-0812R, Dilution: 1/100) were applied as primary antibodies to sections. Then, sections were incubated with the secondary antibody, expose mouse and rabbit specific HRP/DAB detection IHC kit (Abcam: ab80436). As a chromogen, 3,3′-diaminobenzidine (DAB) was used and hematoxylin was preferred for counterstaining. Positive cells were investigated under a light microscope. Tubular epithelium and interstitium were evaluated for IL-1β and TNF-α immunopositivity. Immunopositivity was evaluated as follows: none (0), mild (1), moderate (2), and intense (3).

Statistical analysis

The IBM SPSS 20.0 package program was used, and the data were analyzed by a one-way ANOVA test. Tukey test was preferred for intergroup comparisons. The results were demonstrated as mean±standard deviation (SD). The differences were admitted significant when $p<0.05$. IHC results were determined by the Kruskal–Wallis test followed by a corrected Mann–Whitney U test. The results were demonstrated as mean±standard error (SE). The differences were admitted significant when $p<0.05$.

Table 1. Comparison of TAS, TOS, OSI, SOD, MPO, and MDA parameters among the experimental groups

Experimental groups (n=8)	TAS (mmol/L)	TOS (µmol/L)	OSI (arbitrary unit)	SOD (U/mg protein)	MPO (U/g protein)	MDA (µmol/g protein)
Sham	2.28±0.28	8.06±0.56	0.35±0.02	427.28±51.17	36696.45±12441.21	76.62±9.21
I/R	2.06±0.25	11.80±1.63[a]	0.58±0.12[a]	198.23±17.76[a]	73603.47±13567.54[a]	1116.66±8.39[a]
Low-dose Ura	2.20±0.30	8.77±1.16[b]	0.40±0.10[b]	330.83±24.21[b]	48676.90±10191.79[b]	86.06±10.78[b]
High-dose Ura	2.52±0.31	8.33±0.88[b]	0.33±0.05[b]	427.49±48.21[b]	34827.32±8872.32[b]	76.80±10.09[b]

TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; SOD: Superoxide dismutase; MPO: Myeloperoxidase; MDA: Malondialdehyde. [a]P<0.001 compared with the sham group. [b]P<0.001 compared with the I/R group.

Table 2. Comparison of experimental groups according to IL-1β and TNF-α immunopositivity

Experimental groups (n=8)	IL-1β immunopositivity	TNF-α immunopositivity
Sham	0.12±0.12[a]	0.25±0.16[a]
I/R	2.87±0.12[b]	2.75±0.16[b]
Low-dose Ura	2.25±0.36[b]	1.62±0.26[c]
High-dose Ura	1.12±0.29[c]	1.25±0.36[c]

Different superscript letters show differences between the groups.

RESULTS

Biochemical results

TAS, TOS, MDA, SOD, and MPO concentrations were determined. In the I/R group, TAS and SOD levels declined while MDA, MPO, and TOS values increased when compared with the sham group. The SOD level increased in the low-dose Ura group, and a significant decrease was observed in TOS, MDA, and MPO values compared with the I/R group. Statistical significance continued in the high-dose Ura group. No significant change in TAS value was observed in either group (Table 1).

IHC results

IL-1β and TNF-α immunopositivity was not observed in the sham group (Fig. 1a). The most intensive IL-1β immunopositivity was in the I/R group, and the Ura low-dose group also performed intense immunopositivity (Fig. 1b, 1c and Table 2). On the other side, IL-1β immunopositivity was mild in the high-dose Ura group (Fig. 1d and Table 2). Besides, IL-1β and TNF-α immunopositivity were also most intensive in the I/R group (Fig. 1b and Table 2), and these parameters decreased in low-dose Ura and high-dose Ura groups (Fig. 1c, 1d and Table 2).

DISCUSSION

In this study, we created an I/R injury in the kidney. We examined the effects of this damage and the possible curative effects of Ura at different doses by molecular and histochemical methods. Our study is the first study in the literature on this aspect. According to our results, the applied experimental model caused histological and bio-

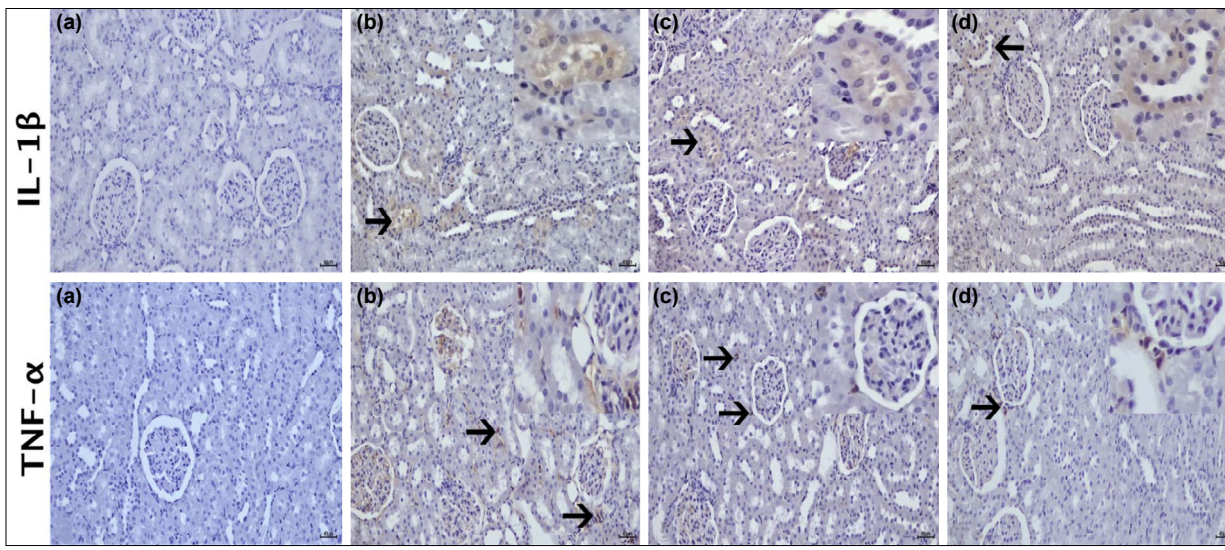

Figure 1. (a) Sham group: normal appearance. **(b)** I/R group: intense IL-1β immunopositivity in the tubular epithelium (arrow) and intense TNF-α immunopositivity in the interstitium (arrow). **(c)** Low-dose Ura group: intense IL-1β immunopositivity in the tubular epithelium (arrow) and mild TNF-α immunopositivity in the interstitium (arrow). **(d)** High-dose Ura group: mild IL-1β immunopositivity in the tubular epithelium (arrow) and mild TNF-α immunopositivity in the interstitium (arrow). IHC, 20× magnification.

chemical damage, and the damage was significantly alleviated with Ura treatment. No side effects were observed in the tissues with both dosages. While the TAS level did not change in both dose treatments, other parameters changed in the direction of reducing oxidant damage. According to the results of the IHC examination, IL-1β immunopositivity was less in the high dose-Ura group, but TNF-α levels were similar in both Ura groups.

I/R-related tissue injury may occur in many clinical situations such as cardiac infarction, stroke, and AKI.[1] Several conditions such as oxidative stress, inflammation, and apoptosis contribute to I/R pathogenesis.[31] Renal I/R injury occurs in case of reperfusion following the recovery of blood flow. Reperfusion aggravates renal injury by triggering an inflammatory cascade and enhancing the generation of ROS and cytokines.[32,33]

The data from several studies suggest that I/R injury is regulated by various mechanisms which cause lipid peroxidation, ROS generation, and oxidative stress.[34] Free oxygen radicals enhance lipid peroxidation, and MDA is a lipid peroxidation product that is used for the evaluation of oxidative stress.[35] I/R injury increased MDA level, but antioxidant mechanisms including SOD prevented harmful effects of MDA.[36] In the current study, Ura treatment diminished MDA levels in treatment groups.

I/R injury pathogenesis includes oxidative stress and inflammation, which lead to cell death. Therefore, various molecules demonstrating antioxidative, anti-inflammatory, and antiapoptotic properties are appropriate protective agents against I/R injuries.[37] Several antioxidant enzymes including SOD remove ROS and thus decline I/R-induced tissue injury.[38] Antioxidant agents may prevent oxidative damage induced by I/R.[39] In the current study, I/R decreased SOD activity, and low- and high-dose Ura treatment reversed this parameter. TAS measurement provides the evaluation of all antioxidant levels in a biological sample.[40] TOS to TAS ratio is represented as OSI, and it is an indicator of oxidative stress.[41] With Ura treatment, OSI has changed significantly in favor of antioxidants.

Ura has an antihypertensive effect through binding α1-adrenoreceptor and serotonin receptors.[42,43] Ura, as a vasodilator, has been suggested as antihypertensive agent.[44] Ura reduces vascular tone, prompts vasodilatation, and causes low blood pressure.[45] As studies showing the effect of Ura directly on cytokines are limited in the literature, this study may lead to other studies on this aspect. In a testicular torsion model, 0.5 mg/kg Ura administration prevents oxidant damage by decreasing MDA value and increasing SOD and GPx levels.[26] Similar to a previous study, protective effects occurred with 0.5 mg/kg and 5 mg/kg doses of Ura administration in our study.[25]

We assessed the renal tissue to search for the potential protective effects of Ura against renal injury induced by I/R and observed that oxidative stress declined with Ura. Thereby, Ura may be a new agent in the treatment of I/R.

CONCLUSION

Ura prevented I/R-induced renal injury with its antioxidant and anti-inflammatory properties.

Ethics Committee Approval

This study approved by the Atatürk University Animal Experiments Local Ethics Committee (Date: 30.03.2018, Decision No: 58).

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: A.T., E.E., D.G.E.; Design: M.C.G., S.D.; Supervision: D.G.E., M.C.G.; Fundings: D.G.E., S.D.; Materials: A.T., E.E.; Data: M.C.G., S.D., S.Ç.; Analysis: A.T., E.E., D.G.E., S.Ç.; Literature search: D.G.E., M.C.G.; Writing: D.G.E., M.C.G., A.T., E.E., S.Ç.; Critical revision: A.T., D.G.E.

Conflict of Interest

None declared.

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Renal İskemi Reperfüzyonu ile İlişkili Böbrek Hasarına Karşı Urapidil'in Yararlı Etkileri

Amaç: Burada urapidilin (Ura), iskemi reperfüzyon (I/R) ile oluşan böbrek hasarına karşı potansiyel koruyucu etkileri incelenmiştir.

Gereç ve Yöntem: Bu amaçla deney hayvanları sham, I/R, I/R+Ura 0.5 mg/kg ve I/R+Ura 5 mg/kg gruplarına ayrıldı. Total antioksidan statüsü (TAS), süperoksid dismutaz (SOD), total oksidan statüsü (TOS), miyeloperoksidaz (MPO), oksidatif stress indeksi (OSI) ve malondialdehit (MDA) parametreleri belirlendi.

Bulgular: I/R grubunda MDA, TOS, MPO ve OSI değerleri yükselirken TAS ve SOD seviyeleri azaldı. Ura tedavisi bu parametreleri tersine çevirdi. Ek olarak interlökin-1 beta (IL-1β) ve tümör nekrozis-alfa (TNF-α) immünopozitifliği I/R grubunda şiddetli idi, ancak Ura uygulaması bu değerleri azalttı.

Sonuç: Mevcut çalışma sonuçları, Ura'nın I/R menşeili böbrek hasarına karşı oldukça etkili olduğunu göstermiştir.

Anahtar Sözcükler: Böbrek; iskemi reperfüzyon; oksidatif stres; sıçan; urapidil.