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Brief Communication

Protective Role of Angiotensin Type 1 Receptor Blockade in 4/6 Nephrectomized Male and Female Rats

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Abstract

Background: Chronic kidney disease associated with serious morbidity and mortality rate while it is affected by renin-angiotensin system. The effects of losartan as angiotensin II Type 1 receptor antagonist on renal functional in 4/6 nephrectomized rats was evaluated. **Methods:** Twenty-six male and female Wistar rats underwent 4/6 nephrectomy, and the animals from each gender were randomly divided into two groups which treated with vehicle and losartan (10 mg/kg/day for 1 week). The parameters related to kidney function were measured. **Results:** Creatinine (Cr) clearance and urine flow were improved in losartan-treated group significantly ($P < 0.05$). The serum level of blood urea nitrogen and Cr and kidney tissue damage score and sodium urinary output ($U_{Na}V$) did not alter. However, losartan decreased percentage of sodium excretion (E_{Na} %) in both genders insignificantly. **Conclusions:** Losartan may improve renal function in 4/6 nephrectomized male rats.

Keywords: *Losartan, nephrectomy, rat*

Introduction

The renin-angiotensin system (RAS) has an important role in the progression of renal disease and kidney pathomorphologic alteration. These changes include tubulointerstitial fibrosis, tubular atrophy, inflammation, and glomerulosclerosis.[1] The major biologic actions of angiotensin II (Ang II) is mediated by Ang II Types 1 and 2 receptors (AT1R and AT2R).[2] Pro-inflammatory effects, stimulation of tubular transport, vasoconstriction, aldosterone release, and growth stimulatory actions, are mediated by AT1R,[2,3] whereas AT2R activation is vasodilation through the formation of bradykinin and nitric oxide.[4] In addition, the studies have demonstrated that RAS functions act gender dependently.[5] RAS and its receptor blockades plays an important role in decreasing chronic renal failure (CRF) progression and improve kidney tissue damage.[6,7] The role of losartan is reported in acute and CRF;[8,9] however, its gender-related effects is not completely known. Therefore, this study was designed to determine the effect of AT1R antagonist (losartan) on 4/6 nephrectomized male and female rats.

Methods

Animals

A total of 26 male and female Wistar rats (Animal Center, Isfahan University of Medical Sciences, Isfahan, Iran) were used in this research study. The rats were housed at a temperature of 23°C–25°C with a 12 h light/dark cycle and they had free access to water rat chow. All experiments were approved by the Isfahan University of Medical Sciences Ethics Committee.

Experimental protocol

Rats were anesthetized with chloral hydrate (450 mg/kg, ip) and underwent 4/6 nephrectomy (4/6 NX) by the removal of the right kidney and ablation approximately of one-thirds of the left kidney (lower pole). The rats from each gender were randomly divided into two groups: 4/6 nephrectomized group (named vehicle group) and 4/6 nephrectomized losartan-treated group (named losartan group).

Losartan (10 mg/kg/day. ip) and vehicle were administrated 2 h before surgery and continued daily for 1 week. At the last day of experiment, the rats were placed in metabolic cages for 6 h to collect urine volume and urine flow (UF). Finally, blood samples were obtained, and the animals were sacrificed humanly.

The testis, uterus, and remnant kidney tissues were removed and weighted, and the kidney tissue was fixed in 10% formalin embedded in paraffin for histopathological

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staining. The hematoxylin and eosin stain was applied to examine the tissue injury. Kidney tissue damage score (KTDS) was evaluated by the presence of tubular atrophy, hyaline cast, debris, and vacuolization as 1–4 while zero score was assigned to normal tissue.

Measurements

The serum and urine sodium concentrations were determined by flame photometer. The serum levels of creatinine (Cr) and blood urea nitrogen (BUN) were measured by autoanalyzer (Technicon, Ireland Ltd.) using Pars Azmoon Kits (Tehran, Iran). The serum nitrite level was measured by Griess method.

Statistical analysis

Data are expressed as mean ± standard error of mean. Statistical analysis was performed using Kruskal–Wallis and Mann–Whitney test pathology data. Comparisons among independent samples were analyzed by Student's *t*-test. Statistical significance was accepted when $P \leq 0.05$.

Results

UF and Cr clearance were increased significantly in losartan-treated groups in male rats ($P < 0.05$), but such observations were not observed in female animals. Losartan attenuated the body weight change (ΔBW) in female significantly ($P < 0.05$) [Table 1]. The serum levels of Cr, BUN and nitrite, and tissues (kidney, testis, and uterus) weight per 100 g body weight, KTDS, and sodium urinary output per gram kidney tissue ($U_{Na}V$) were not significantly different between losartan- and vehicle-treated groups in both genders [Figure 1 and Table 1]. In addition, the percentage of sodium excretion (E_{Na}%) was decreased in losartan groups insignificantly.

Discussion

Some clinical and experimental animal studies have found evidence for the upregulation of RAS system in the progression of renal disease,[10,11] and AT1R blockade may improve impaired kidney.[6,12] The effects of losartan through decreasing of inflammation, blood pressure, platelet activation and aggregation, and increasing of vasodilation and glomerular filtration rate (GFR) have been reported.[13-15] In the present study, we showed the effects of losartan on renal function in 4/6 nephroctomized male and female rats, and the major findings indicated that losartan increased Cr clearance and UF in both genders; however, it was significant only in male rats. The increased UF in losartan-treated male rats was not related to sodium excretion since E_{Na} % in losartan group was lower than vehicle-treated group [Figure 1]. It seems that the reason is related to GFR increasing by losartan while Cr clearance

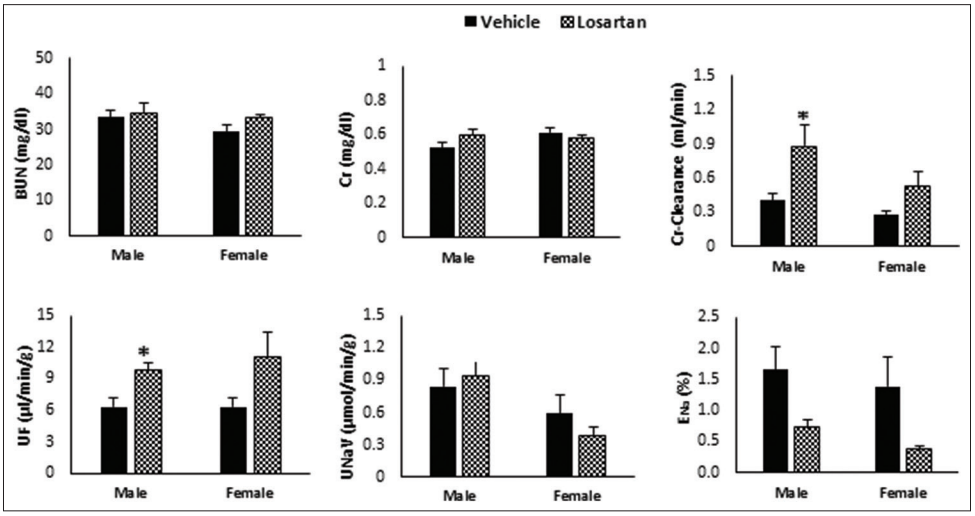

Figure 1: The serum levels of blood urea nitrogen and creatinine, and creatinine clearance, urine flow, sodium urinary output per gram kidney tissue, and percentage of sodium excretion (ENa%) in losartan- and vehicle-treated 4/6 nephroctomized male and female rats. Star (*) represents significant difference from vehicle group in the same gender ($P < 0.05$)

Table 1: Kidney tissue damage score, remnant kidney weight/100 g body weight, uterus weight/100 g body weight, testis weight/100 g body weight,body weight change (g), and serum nitrite (µmole/l) in 4/6 nephrectomized animals

Gender	Group	KTDS	KW/100 g BW	UW/100 g BW	TW/100 g BW	BW change	Serum nitrite
Male	Vehicle	1.16±0.2	0.47±0.01		1.21±0.06	−10±2.03	2.67±0.5
	Losartan	1.41±0.2	0.47±0.03		1.12±0.03	−11.6±6.06	2.91±0.8
Female	Vehicle	1.66±0.1	0.43±0.01	0.04±0.01		−19.3±4.6	2.32±0.3
	Losartan	1.7±0.2	0.46±0.02	0.04±0.01		−12.8±3.7*	3.77±0.6

*Significant difference from vehicle group in the same gender, $P<0.05$. Values are means±SEM. KTDS=Kidney tissue damage score, SEM=Standard error of mean, KW=Kidney weight, BW=Body weight, UW=Uterus weight, TW=Testis weight

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was also increased. UF and Cr clearance also were increased in female rats treated with losartan insignificantly. Possibly, the animal sample size was not large or the dose of losartan was not enough since an experimental study showed that renal protection by losartan was dose-related.[16] Kidney functional factors such as BUN and Cr did not alter. Our findings corroborate the previous report that has shown neither BUN nor Cr altered after 8-week losartan therapy (20 mg/kg/day) on isolated mesenteric resistance arteries in 5/6 nephrectomized rats.[17] It is concluded that losartan can improve Cr clearance, UF and E_{Na} % without alteration of BUN and Cr in 4/6 nephrectomized in male. More studies in female with different doses of losartan are needed.

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Conflicts of interest

There are no conflicts of interest.

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