Original Article

The Effect of Angiotensin II Type 1 Receptor Antagonist on Age-Related Differences in Renal Vascular Responses to Angiotensin II in Male and Female Rats

Fatemeh Eshraghi-Jazi[1], Mehdi Nematbakhsh[1,2]

[1]Water and Electrolytes Research Center, Medical School, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Physiology, Medical School, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Advancing age could influence renin angiotensin system components, especially angiotensin type 1 receptor (AT1R). This study examined the effect of AT1R antagonist, losartan, on age-related differences in renal vascular responses to angiotensin II in male and female rats.

Materials and Methods: Forty-eight anesthetized male and female rats (8–12 and 24–28 weeks age ranges) were subjected to catheterize. Then, the responses of mean arterial pressure (MAP), renal perfusion pressure (RPP), renal blood flow (RBF), and renal vascular resistance (RVR) to angiotensin II with or without losartan were determined and evaluated.

Results: There were not significant differences in the basal values of MAP, RPP, RBF, and RVR in males. However, it was observed significant difference in RVR in females ($P < 0.05$). The blockade of AT1R attenuated basal MAP and RPP in all the groups ($P < 0.05$). The infusion of losartan altered basal RVR and RBF values in female groups ($P < 0.05$). Moreover, losartan eliminated vasoconstrictor responses to angiotensin II in female groups ($P < 0.05$). Also, losartan induced significant vascular responses to angiotensin II in male groups ($P < 0.05$).

Conclusions: Losartan could maintain RBF changes in response to angiotensin II in both 8–12- and 24–28-week females. Losartan enhanced the RBF response to angiotensin II in 8–12-week males, but not in 24–28-week males. It seems that females (not males) in various age ranges are resistance against RBF changes by acutely increased angiotensin II.

Keywords: Age, angiotensin II, gender, Losartan, rat, renal blood flow

Address for correspondence: Prof. Mehdi Nematbakhsh, Water and Electrolytes Research Center/Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: nematbakhsh@med.mui.ac.ir
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Introduction

Sexual dimorphism has been considered influencing the renal function in both pathophysiological and physiological conditions.[1,2] Age is also known as an important factor in animal experiments that affects kidney function.[3,4] In addition, sexual dimorphism and age may participate in the responses of the renin angiotensin system (RAS) in age- or sex-associated experiments.[5,6] RAS has an important peptide, angiotensin II (Ang II), which involves the regulation of blood pressure and body fluid volume. Ang II acts via the Ang II type 1 receptor (AT1R) and the Ang II type 2 receptor (AT2R).[7] AT1R exhibits vasoconstrictor responses, while AT2R has vasodilator effects.[8,9] Ang II receptors are affected by age and gender. It is reported that the pathway of angiotensin-converting enzyme/Ang II/AT1R enhances in male sex, but AT2R has more expression in females than males.[10] With age, the AT1R/AT2R ratio increases in male

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rats,[11] and estrogen therapy reduces Ang II pressor responses in females.[12] AT1R as a target receptor is proposed in studies associated with age, and losartan as one of the AT1R inhibitors can antagonize age-associated consequences.[13] Several studies have evidenced the effects of AT1R blockade on kidney and RAS in different animal models.[14-18] However, the effect of AT1R blockade is not well understood in renal hemodynamic responses to Ang II in male and female rats with various age ranges. Therefore, the current study investigated the role of AT1R on renal hemodynamic responses to Ang II infusion in 8–12- and 24–28-week-old male and female rats.

Materials and Methods

Animals

In the current study, 8–12-, and 24–28-week Wistar male (251.21 ± 6.35 g and 313 ± 9.99 g, respectively) and female (169.69 ± 4.20 g and 206.80 ± 5.39 g, respectively) rats were used. All animals were housed in the animal room of the Water and Electrolytes Research Center with a temperature of 23–25°C and a 12-h light/12-h dark cycle. Also, the animals had free access to water and food. All experimental procedures were approved by the ethics committee of Isfahan University of Medical Sciences (Code # IR. MUI.RESEARCH. REC. 1399. 564). To control age, the pregnant females were separated and taken care of until delivery. The details, such as birthday and gender, were labeled on the cages. After weaning, male and female offspring were randomly arranged into the age ranges of 8–12 and 24–28 weeks, and housed to reach the target age.

Chemical agents

In the current study, chemicals included urethane (Sigma; USA), losartan (Pars Darou, Iran), Ang II (Sigma, USA), heparin sodium ampoule 5000 IU/mL, and saline solution 0.9% (Darou Pakhsh, Iran) and the lubricating gel of water-soluble (Toliddaru, Iran) were provided and used.

Experimental groups

The animals were randomly assigned into the eight experimental groups as follows: group 1 (n = 7), 8–12-week males receiving vehicle before (30 min before Ang II injection) and along with Ang II injection; group 2 (n = 7), 8–12-week males receiving losartan before (30 min before Ang II injection) and along with Ang II injection; group 3 (n = 6), 24–28-week males receiving vehicle before (30 min before Ang II injection) and along with Ang II injection; group 4 (n = 5), 24–28-week males receiving losartan before (30 min before Ang II injection) and along with Ang II injection; group 5 (n = 6), 8–12-week females receiving vehicle before (30 min before Ang II injection) and along with Ang II injection; group 6 (n = 7), 8–12-week females receiving losartan before (30 min before Ang II injection) and along with Ang II injection; group 7 (n = 5), 24–28-week females receiving vehicle before (30 min before Ang II injection) and along with Ang II injection; group 8 (n = 5), 24–28-week females receiving losartan before (30 min before Ang II injection) and along with Ang II injection.

Surgical procedure

The animals anesthetized with urethane (1.7 g/kg dissolved in saline, intraperitoneally)[6] were underwent tracheostomy. After that, the carotid and femoral arteries were isolated. Flexible polyethylene tubes (PE9658 for carotid artery and PE8040 for femoral artery, Microtube Extrusions; Australia) filled with saline-heparin solution were inserted into the arteries. In addition, a polyethylene tube (PE9658) filled with saline solution was inserted into the jugular vein for infusing losartan or vehicle and Ang II. Next, the animals were placed on the right flank, and an incision was made on the left flank by an electrosurgical instrument (Erbe Elektromedizin GmbH; Germany) to avoid bleeding. Then, adipose tissues were pushed to the other side with special care to expose the left kidney. An adjustable occluder was placed around the abdominal aorta for controlling renal perfusion pressure (RPP) during the Ang II infusion. After isolating the left renal artery, a flow probe (Transonic Systems Inc.; USA) connected to a perivascular flowmeter system (TS420, Transonic System Inc; USA) was placed around the renal artery for measuring renal blood flow (RBF). Then, the flow probe was covered by the lubricating gel. Because of surgery and experiment procedures which take long, the tube implanted into the trachea was linked to an oxygen tank to supply oxygen and improve ventilation during the experiment. After ending surgery, the carotid and femoral cannulas were connected to the pressure transducers attached to the power lab system (AD Instruments; Australia) to measure mean arterial pressure (MAP) and RPP.

Experimental design

To reach stable hemodynamic conditions, the animals were monitored continually for at least 30 minutes during the equilibrium phase. The measurements of the last five minutes were considered basal data, and the animals with MAP <80 mmHg or RBF <1 mL/min were excluded from the study. In the next phase named antagonist (Treat), a blouse dose of losartan (5 mg/kg) or vehicle was administrated, pursued by a continuous dose of losartan (5 mg/kg/h) or vehicle via microsyringe pump (New Era Pump systems, Inc; USA).[17,18] Then, Ang II was infused at doses of 30, 300, and 1000 ng/kg/min (each dose for 15 min)[6,19] using a microsyringe pump without stopping the infusion of losartan or vehicle. This phase was nominated as a response to Ang II. The measurements of the last five minutes in the antagonist phase as well as in each dose of Ang II were assessed. At the end of the experiment, the animals were killed humanely, and the kidneys were taken out and weighed rapidly.

Measureable values

In the current study, hemodynamic parameters, including MAP, RPP and RBF, and renal vascular resistance (RVR), were determined. RVR was computed by the RPP/RBF ratio. Also, basal RBF and RVR were normalized based on the left kidney weight. In addition, all hemodynamic parameters in both phases of antagonist and response to Ang II were presented as the percentage of changes.

Statistical analysis

SPSS software, version 20, was used to analyze all the data. The data were expressed as mean ± SEM. An independent *t*-test was used to analyze the basal data of MAP, RPP, RBF, and RVR. Moreover, the analysis of repeated measures followed by the LSD post-test was used to analyze MAP, RPP, RBF, and RVR in both phases of antagonist and response to Ang II. The *P* values ≤ 0.05 were considered statistically significant.

Results

Baseline measurements

The basal values of MAP, RPP, RBF, and RVR were illustrated in Table 1 and measured between two age ranges in each gender (8–12-week males: n = 14 and 24–28-week males: n = 11; 8–12-week females: n = 13 and 24–28-week females: n = 10). There were not any significant differences in the above-mentioned parameters between two age ranges in male sex [Table 1]. Also, significant changes were not observed in the basal values of MAP, RPP, and RBF between 8–12- and 24–28-week females. However, the basal RVR had a significant difference between two age ranges in female sex ($P < 0.05$) [Table 1].

Antagonist (losartan) effect measurements

The infusion of losartan significantly attenuated basal MAP and RPP values in both 8–12- and 24–28-week male groups ($P_{Treat} < 0.05$) [Figures 1a and b]. Moreover, there were similar observations in female groups receiving losartan, regardless of age ($P_{Treat} < 0.05$) [Figures 1e and f]. Basal MAP and RP*P* values were reduced in all groups receiving losartan in comparison to groups receiving vehicle, regardless of age or gender ($P_{Group} < 0.05$) [Figures 1a, b, e, and f]. The infusion of losartan did not alter the basal values of RBF and RVR in male groups [Figures 1c and d]. In contrast, RBF and RVR increased and decreased in 24–28-week female receiving losartan than one receiving vehicle, respectively ($P_{Group} < 0.05$) [Figures 1g and h]. In addition, the 24–28-week female group receiving losartan had an increment in RBF greater than the 8–12-week female group receiving the same treatment ($P_{Group} < 0.05$) [Figure 1g].

Vascular response to Ang II administration

The MAP response to Ang II increased in both age ranges of 8–12 and 24–28 weeks receiving vehicle in each gender significantly ($P_{Dose} < 0.05$) [Figures 2a and e], and the infusion of losartan eliminated the increase in MAP response to Ang II, regardless of age or gender [Figures 2a and e]. Moreover, losartan decreased the response of MAP to Ang II in both male and female genders than ones receiving vehicle, significantly ($P_{Group} < 0.05$). However, age differences did not influence this observation [Figures 2a and e]. Despite adjusting the abdominal aorta by the occluder, there were significant differences in RPP response to Ang II in groups receiving the vehicle ($P_{Dose} < 0.05$) [Figures 2b and f]. It is notable that because the infusion of losartan reduced the RPP response to Ang II below the values of the antagonist phase in all male and females groups, occluder was not required for regulating RPP in the phase of response to Ang II [Figures 2b and f].

The values of RBF and RVR in response to Ang II without blocking AT1R decreased and increased in both male and female genders, respectively, regardless of age ($P_{Dose} < 0.05$) [Figures 2c, d, g and h]. The blockade of AT1R not only prevented the decreasing of RBF in response to Ang II in 8–12-week males compared to the age-matched male receiving vehicle but also increased this response ($P_{Group} < 0.05$) [Figure c]. Interestingly, age could influence the response of RBF to Ang II in male sex, when AT1R was blocked by losartan. In other words, losartan increased RBF in response to Ang II in 8–12-week males, but not in 24–28-week males ($P_{Group} < 0.05$) [Figure 2c]. Also, there were significant differences in RBF response to Ang II between age-matched females without age-related differences ($P_{Group} < 0.05$) [Figure 2g]. A similar trend was observed in RVR response to Ang II in female groups ($P_{Group} < 0.05$) [Figure 2h]. In contrast, the presence of AT1R antagonist was able to make a significant change in the RVR responses to Ang II only in 8–12-week males when compared to the age-matched male receiving vehicle ($P_{Group} < 0.05$). This observation did not occur in the 24–28-week male groups [Figure 2d].

Discussion

The current study attempted to clarify the effect of AT1R blockade or nonblockade on renal vascular responses to Ang II administration between two age ranges of 8–12 and

Table 1: Baseline values of mean arterial pressure (MAP), renal perfusion pressure (RPP), renal blood flow (RBF), and renal vascular resistance (RVR) in 8–12- and 24–28-week animals in both genders. Data were expressed as mean±SEM. The values of RBF and RVR were presented based on per gram of left wet kidney weight

Gender	Age (Week)	MAP (mmHg)	RPP (mmHg)	RBF (mL/min/g left KW)	RVR (mmHg/mL/min/g left KW)
Male	8-12	86.54±2.99	80.32±3.53	1.68±0.13	51.23±4.24
	24-28	87.82±4.32	78.54±3.58	1.39±0.14	70.81±16.04
	P	0.80	0.73	0.16	0.20
Female	8-12	87.93±3.01	81.21±4.06	2±0.15	43.32±3.89
	24-28	82.77±2.46	72.99±3.49	2.29±0.15	32.78±2.30
	P	0.21	0.15	0.21	0.04

An independent *t*-test compared the baseline values between 8–12- and 24–28-week animals in each gender

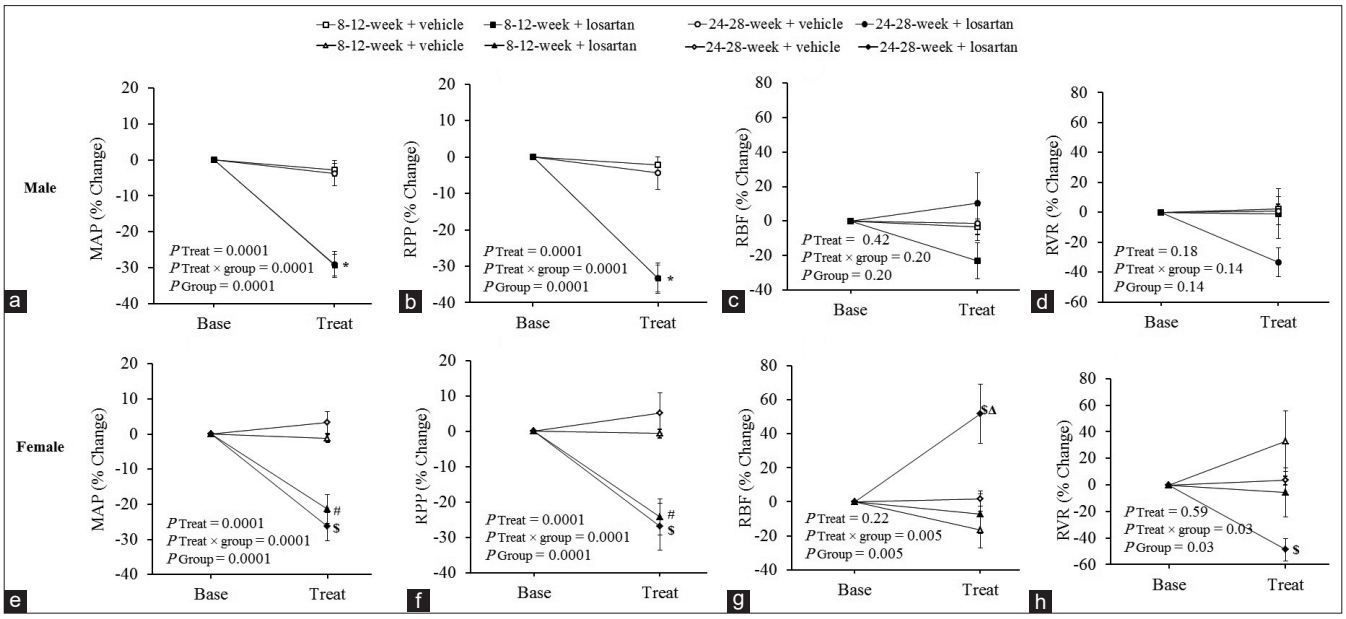

Figure 1: The effect of losartan infusion on hemodynamic responses in the antagonist phase in both age ranges of 8–12 weeks and 24–28 weeks in each gender. The parts a–d illustrate mean arterial pressure (MAP), renal perfusion pressure (RPP), renal blood flow (RBF), and renal vascular resistance (RVR) in male groups, respectively. The parts e-h illustrate MAP, RPP, RBF, and RVR in female groups, respectively. Data were expressed as mean ± SEM. $^{*}P_{Group} < 0.05$, $^{\#}P_{Group} < 0.05$, $^{\$}P_{Group} < 0.05$, and $^{\Delta}P_{Group} < 0.05$ indicate the significant differences in comparison to the respective group receiving vehicle, 8–12-week group receiving vehicle, 24–28-week group receiving vehicle, and 8–12-week group receiving losartan, respectively

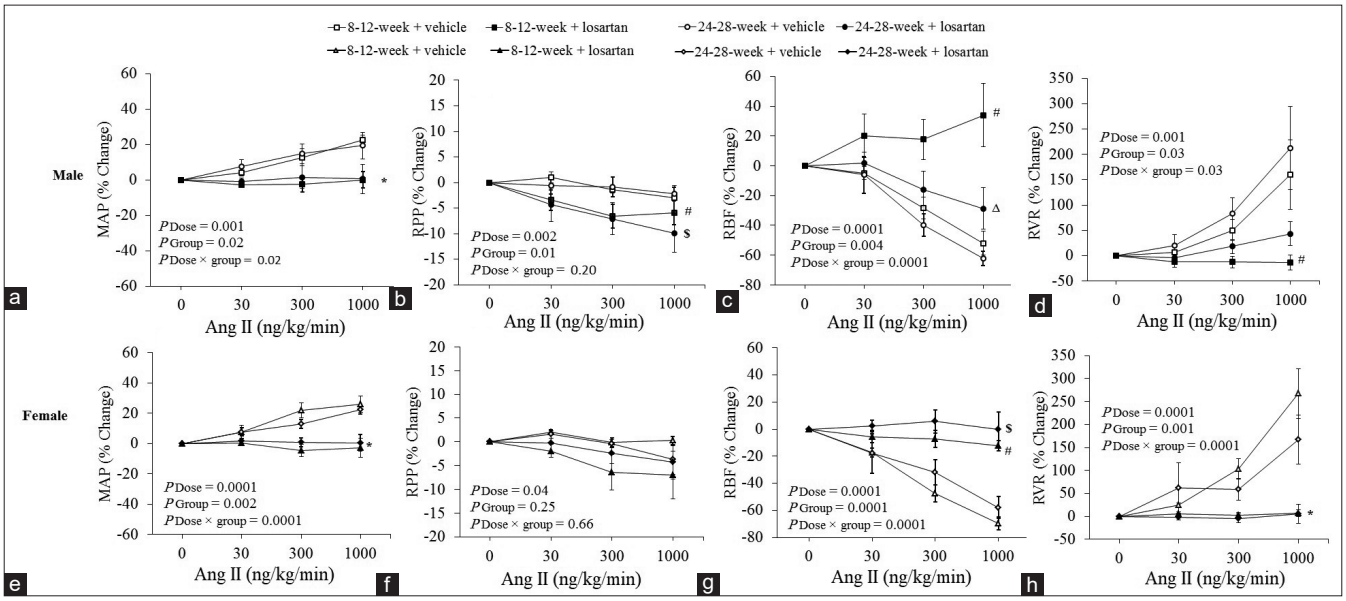

Figure 2: The effect of losartan infusion on the hemodynamic responses to angiotensin II (Ang II) graded doses in both age ranges of 8–12 weeks and 24–28 weeks in each gender. The parts a–d illustrate mean arterial pressure (MAP), renal perfusion pressure (RPP), renal blood flow (RBF), and renal vascular resistance (RVR) in male groups, respectively. The parts e-h illustrate MAP, RPP, RBF, and RVR in female groups, respectively. Data were expressed as mean ± SEM. $^{*}P_{Group} < 0.05$, $^{\#}P_{Group} < 0.05$, $^{\$}P_{Group} < 0.05$, and $^{\Delta}P_{Group} < 0.05$ indicate the significant differences in comparison to the respective group receiving vehicle, 8–12-week group receiving vehicle, 24–28-week group receiving vehicle, and 8–12-week group receiving losartan, respectively

24–28 weeks in both male and female rats. The study reached several important points, which were discussed one by one.

First, the blockade of AT1R by losartan decreased the basal values of MAP and RPP in all groups, regardless of age and gender. Losartan is well known as an antihypertensive agent in clinic,[20,21] and it is widely used in experimental studies.[13,18,22,23] Several experiments have revealed that the administration of losartan decreased the basal values of MAP and RPP in both male and female animal models with various age ranges,[16-18,22,24,25] which confirms the current findings. Also, a clinical study in healthy young men and women showed that the blockade of AT1R by irbesartan, another antagonist of

AT1R, decreased MAP without gender difference.[26] Therefore, the current study revealed that the gender- and age-related differences did not influence the effect of the blockade of AT1R on MAP and RPP responses. Whereas, Yanes *et al*.[16] reported that the administration of losartan attenuated MAP in aged males more than age-matched females, probably due to the chronic administration of losartan. The infusion of losartan affected the basal renal vascular responses only in females, but not in males. In contrast with this study, Baylis[27] revealed that the acute administration of losartan did not influence hemodynamic values in 3–5-month male Sprague Dawley rats, whereas 19–22-month male group exhibited renal hemodynamic responses such as renal vasodilation, increasing renal plasma flow (RPF), and urine flow. In another investigation, Tank *et al*.[25] exhibited an increase in RPF as well as the enhancement of basal GFR in a 15-month male group receiving losartan compared to treatment-matched 3-month ones. Maybe various age ranges participate in this regard. The 24–28-week animals used in the current study had a lower age range than ones used in Baylis's[27] or Tank's[25] studies, which should not be neglected.

Second, the blockade of AT1R by losartan could eliminate the increasing MAP in response to Ang II infusion in both age categories, regardless of gender, which confirmed the blockade of AT1R. In line with this observation, Yanes *et al*.[16] reported that losartan similarly abolished the MAP response to Ang II bolus doses in 16-month-old male and female hypertensive rats. Other studies also have evidenced the suppressing effects of losartan on the pressor response to Ang II in animal models.[24,25]

Third, losartan removed the decreasing and increasing responses of RBF and RVR to Ang II in 8–12-week male group, respectively. In addition, losartan enhanced the values of RBF in response to Ang II in this group. However, the blockade of AT1R did not show a similar RBF response to Ang II in the 24–28-week male group. Previously, it has been documented that losartan by blockade of AT1R is able to enhance and decrease RBF and RVR in response to Ang II in adult animals, respectively.[18,22,23] Here, there are some possibilities: I. The blockade of AT1R by losartan increased the availability of Ang II for binding to AT2R. In this regard, it was evidenced that the blockade of AT1R enhanced the circulating levels of renin and Ang II in healthy subjects.[26] Therefore, it is possible that the interaction of Ang II and AT2R presents the vasodilator effect, such as antagonizing AT1R effects; II. By blocking AT1R, Ang II especially at the dose of 1000 ng/kg/min can convert to Ang 1-7 which excretes vasodilator effects by binding MasR; III. The blockade of AT1R stimulates the release of endothelial-induced nitric oxide, resulting in the activity of AT2R and bradykinin/NO/cGMP vasodilator cascade.[28] In contrast to the 8–12-week male group, losartan did not increase the response of RBF to Ang II in the 24–28-week male group, even though there was a tendency to decrease. In this regard, Baylis *et al*.[27] suggested that the increased activity of renal Ang II by advancing age alters the regulation of Ang II receptors. Therefore, it is possible that the activity of endogenous Ang II increased in 24–28-week males, and the acute administration of losartan was not able to increase the response of RBF to exogenous Ang II in this group. Perhaps it is required that 24–28-week males receive the increased acute dose of losartan or chronically for blocking more AT1R and improving RBF in response to the Ang II infusion.

The infusion of losartan eliminated the decreasing of RBF and the increasing of RVR in response to Ang II in female groups in both age ranges. Although age could not alter these responses between female groups, and female groups in both age ranges receiving losartan showed an identical trend. In other words, neither 8–12-week nor the 24–28-week female group had no increasing response to Ang II, especially in RBF. It is notable that the 24–28-week-old females studied in this research were in the pre-menopausal stage, and endogenous estrogen has probably exhibited the protective role against the vasoconstrictor effects of Ang II. Literature has documented the protective effects of estrogen on the cardiovascular system in women, mediated by the release of endothelial nitric oxide as a vasodilator agent.[29] Also, the direct stimulation of AT2R overexpressed in females than males can influence the sex-related responses to renal hemodynamics as well as the excretory function of the kidney.[30]

Overall, it seems that females are more protective in the pre-menopausal stage than age-matched males against acutely increasing blood pressure, and they are able to endure acute hypertension. Although further experiments must be required to explain the mechanisms involving in the responses to Ang II such as the using of AT2R antagonist.

The current study had a limitation. This study used 8–12- and 24–28-week-old animals. It is recommended to consider a long age interval or assign three or four age categories to both male and female genders in the next investigations.

Conclusion

It is concluded that the blockade of AT1R by losartan could maintain the RBF changes in response to Ang II in both 8–12- and 24–28-week females, but it enhanced the response of RBF to Ang II in 8–12-week males only. It seems that females in the various age ranges are resistant to RBF changes in the conditions of acutely increased Ang II.

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Ethics approval and consent to participate

The animal experiments and procedures were approved by the ethics committee of Isfahan Medical Sciences University (Code # IR. MUI.RESEARCH. REC. 1399. 564).

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Conflicts of interest

There are no conflicts of interest.

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