

The role of Mas receptor on renal hemodynamic responses to angiotensin II administration in chronic renal sympathectomized male and female rats

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Abstract

Background and purpose: Renal hemodynamics is influenced by renal sympathetic nerves and the renin-angiotensin system. On the other hand, renal sympathetic denervation impacts kidney weight by affecting renal hemodynamics. The current study evaluated the role of the Mas receptor on renal hemodynamic responses under basal conditions and in response to angiotensin II (Ang II) in chronic renal sympathectomy in female and male rats.

Experimental approach: Forty-eight nephrectomized female and male rats were anesthetized and cannulated. Afterward, the effect of chronic renal sympathectomy was investigated on hemodynamic parameters such as renal vascular resistance (RVR), mean arterial pressure (MAP), and renal blood flow (RBF). In addition, the effect of chronic sympathectomy on kidney weight was examined.

Findings/Results: Chronic renal sympathectomy increased RVR and subsequently decreased RBF in both sexes. Renal perfusion pressure also increased after sympathectomy in male and female rats, while MAP did not change, significantly. In response to the Ang II injection, renal sympathectomy caused a greater decrease in RBF in all experimental groups, while it did not affect the MAP response. In addition, chronic sympathectomy increased left kidney weight in right nephrectomized rats.

Conclusion and implications: Chronic renal sympathectomy changed systemic/renal hemodynamics in baseline conditions and only renal hemodynamics in response to Ang II administration. Moreover, chronic sympathectomy increased compensatory hypertrophy in nephrectomized rats. These changes are unaffected by gender difference and Mas receptor blocker.

Keywords: Angiotensin II; A779; Renal blood flow; Renal denervation.

INTRODUCTION

Kidneys are innervated by numerous renal afferent and efferent nerves to create communication with the central nervous system. The innervation of the main structural constituents of the kidneys including glomeruli, pelvis, tubules, and blood vessels creates a bilateral neural network that transmits and receives neural signals to and from the brain, respectively (1). Renal sympathetic nerves control renal blood circulation, tubular sodium reabsorption, and renin release; therefore, sympathetic outflow to the kidneys is crucial for fluid and electrolyte regulation, mean arterial pressure (MAP) homeostasis, the

regulation of renal vascular resistance (RVR), and renal hemodynamics (2,3). In this regard, renal denervation (RDN) is well-known as a common method for determining the role of renal sympathetic nerves in regulating renal hemodynamics (3).

The renin-angiotensin system (RAS) is responsible for the regulation of electrolyte balance and blood pressure (4). Also, RAS participates in the physiological and pathophysiological regulation of cardiovascular function (5).

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A locally-independent RAS is expressed in the kidneys, where renin converts angiotensinogen to angiotensin I (Ang I), and Ang I is subsequently broken down to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) (6-8). Ang II performs various physiological and pathophysiological actions such as vasoconstriction, sodium and water retention, inflammation, hypertrophy, fibrosis, and aldosterone secretion through its type 1 receptor (AT1R) (9,10). Conversely, the Ang II type 2 receptor (AT2R) has the opposite impact of AT1R (11). The vasodilator action of the RAS is mediated by angiotensin 1-7 (Ang-(1-7)), which is derived from the hydrolysis of Ang II or Ang I by an enzyme 2 converting angiotensin (ACE2) (12). The stimulation of the Mas receptor (MasR) by Ang-(1-7) results in vasodilator, natriuretic, and diuretic effects (13-15). A779 is a specific Ang-(1-7) antagonist (MasR blocker) (16).

Excitatory interactions exist between the sympathetic nervous system and Ang II. The renal sympathetic nerve principally determines the release of renin mediated by the β 1-adrenergic receptor, which is a contribution for controlling the circulating Ang II levels. Consequently, RDN decreases circulating renin and Ang II activity (17,18). In addition, Ang II increases the neurotransmission of the sympathetic nervous system by provoking the presynaptic release of epinephrine and norepinephrine, enhancing ganglionic transmission, and prohibiting the reuptake of norepinephrine in nerve terminals. However, the physiological significance of the sympathetic system for the pressor impacts of exogenous Ang II stays controversial (5). Furthermore, there is a significant difference between men and women in the basal function of the sympathetic nervous system and the RAS components (19-21). According to studies, men have greater basal sympathetic-induced vasoconstriction than women in most vascular beds (19), and the ACE/Ang II/AT1R pressor pathway increases in men (22).

On the other hand, although the kidneys try to maintain renal perfusion within a certain limit, significant fluctuations in renal blood flow (RBF) occur due to renal nerve effects and hormonal influences, among others (23).

Changes in renal perfusion pressure (RPP) can majorly impact renal excretory function, renin release, and blood pressure (24). Decreased RPP initiates several compensatory mechanisms that maintain RBF. Initial responses include increased systemic arterial pressure to improve renal perfusion and RBF (25). However, the kidneys are the predominant long-term regulators of arterial pressure; thus, an increase in RPP results in decreased sodium reabsorption and increased sodium excretion. High blood pressure occurs only when the relationship between arterial pressure and sodium excretion shifts toward higher pressures (26-28).

In addition, kidney volume is related to kidney function (29). When the normal kidney is removed, the glomerular filtration rate (GFR) of the contralateral kidney rapidly increases (29). It is assumed that the contralateral kidney can detect the amount of functional changes caused by ipsilateral kidney removal and respond with appropriate renal hypertrophy to enable kidney hyperfiltration (30). The degree of compensatory hypertrophy is proportional to the combination of circulatory factors such as RVR (31).

The objective of the present study was to evaluate the impact of chronic renal sympathectomy on renal hemodynamics in male and female rats under normal conditions and when the Ang II trigger was applied. In addition, as regards long-term renal sympathectomy resulted in changes in renal hemodynamics and kidney weight may indicate possible changes in the expression and interaction of receptors as well as vessel structure. Therefore, the current study also investigated the role of MasR in hemodynamic responses to Ang II in sympathectomized Wistar male and female rats.

MATERIALS AND METHODS

Animals

In the present study, 48 male and female Wistar rats (150 - 200 g) were provided by the Animal House of the Water and Electrolyte Research Center of Isfahan University of Medical Sciences. Rats were maintained at 23 - 25 °C with a 12-h light/dark cycle,

allowing them one week to adapt. Furthermore, rats were provided with free access to water and rat chow. This protocol was verified by the Ethical Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.024), and all experiments were conducted regarding the National Institutes of Health Guide for the Care and Use of Laboratory Animals. We utilized female rats in the same diestrus sexual phase.

Experimental groups

Animals were randomly divided into eight groups: group 1 (n = 5), female rats with intact renal nerves receiving saline and graded doses of Ang II; group 2 (n = 5), male rats with intact renal nerves receiving saline and graded doses of Ang II; group 3 (n = 5), female rats with intact renal nerves receiving A779 and graded doses of Ang II; group 4 (n = 6), male rats with intact renal nerves receiving A779 and graded doses of Ang II; group 5 (n = 6): female rats under chronic renal sympathectomy receiving saline and graded doses of Ang II; group 6 (n = 6), male rats under chronic renal sympathectomy receiving saline and graded doses of Ang II; group 7 (n = 7), female rats under chronic renal sympathectomy receiving A779 and graded doses of Ang II; and group 8 (n = 8), male rats under chronic renal sympathectomy receiving A779 and graded doses of Ang II.

Surgical procedures and measurements

Surgical preparation

The animals underwent surgery 28 ± 2 days after the right kidney nephrectomy and left kidney sympathectomy. Urethane was used to anesthetize the rats (1.7 g/kg, intraperitoneally; Merck, Germany). The ventilation was

facilitated by the cannulation of the trachea. The left jugular vein was isolated, distally ligated, and cannulated with a polyethylene tube (PE 9658, Microtube Extrusions, New South Wales, Australia) to inject antagonist/vehicle and Ang II. The catheterization of the left femoral and carotid arteries was performed as well. Then, the catheters were connected to a bridge amplifier and a pressure transducer (Scientific Concepts, Melbourne, Australia) to measure RPP and MAP, respectively (Fig. 1). The rats were placed in a lateral position on the table, and their body temperature was maintained at 37 ± 0.5 °C. The left kidney was exposed, and its artery was encircled by an ultrasound flow probe (Transonic MA0.7PSB, Flow probe, USA) connected to a compatible flowmeter (T402, Transonic Systems Inc., New York, USA) to measure RBF. An adjustable clamp was placed around the aorta above the renal artery during Ang II infusion to maintain normal RPP levels. During the experiment, a data collection system continuously collected MAP, RPP, and RBF (PowerLab, AD Instrumentation, Sydney, Australia). RVR was calculated by dividing RPP to RBF (Fig. 2).

Unilateral nephrectomy

The rats were anesthetized for nephrectomy. The right kidney was exposed through a small dorsolateral incision. The fat surrounding the kidney was delicately manipulated for preventing any adrenal gland damage. Then, renal vessels and nerves were ligated in the hilum. After removing the kidney, its weight was immediately determined. Finally, the incision was sutured, and the animal was allowed to regain consciousness (32) (Fig. 3A).

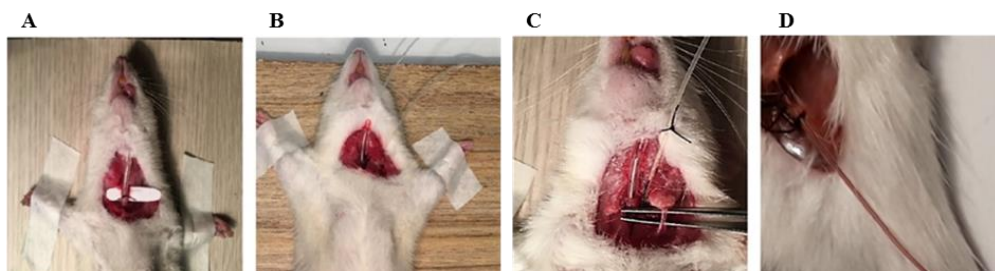


Fig. 1. The catheterization procedure in a rat. (A) Tracheal catheterization; (B) carotid artery catheterization; (C) vena cava catheterization; and (D) femoral artery catheterization.

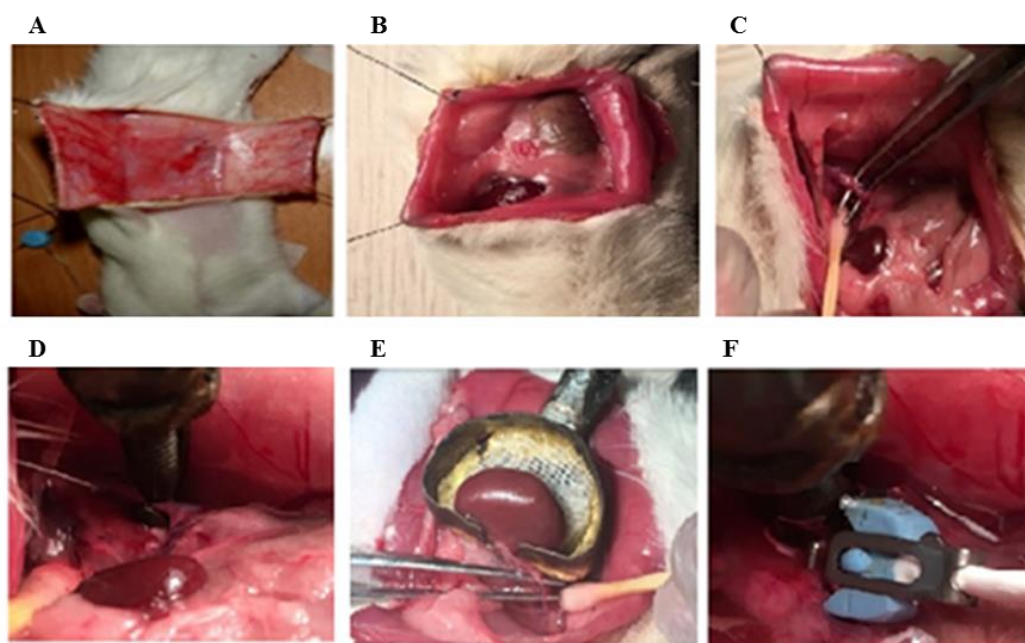


Fig. 2. The isolation producers of kidney and renal artery. (A) Transverse section of the side; (B) location of the kidney and viscera; (C) isolation of abdominal aorta; (D) placing the adjustable clamp around the abdominal aorta; (E) putting the kidney into the kidney cup and separating the artery from the vein of the kidney; and (F) placing the probe around the renal artery.

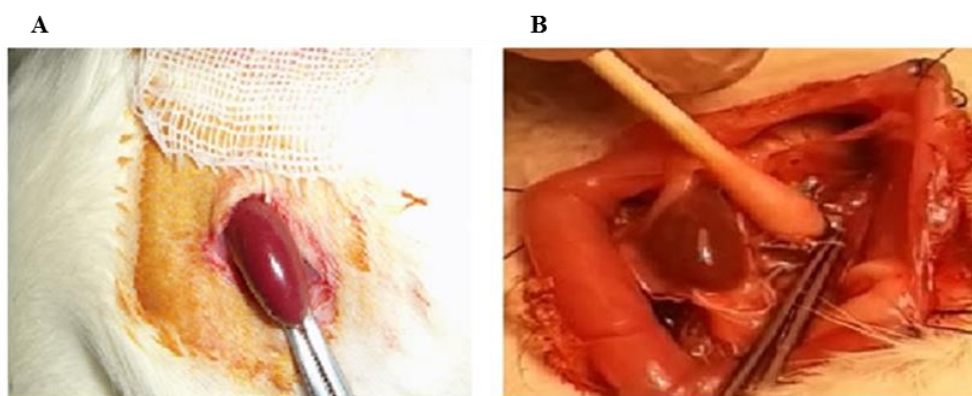


Fig. 3. Nephrectomy and sympathectomy. (A) Exposing the right kidney for nephrectomy; (B) cutting the afferent and efferent nerves of left kidney.

Renal denervation procedure

After the right nephrectomy surgery, the animal left side was sterilized and cut to expose the ureter, artery, vein, and nerves of the kidney. All visible renal nerves were meticulously isolated, dissected, and cut under the microscope. To make sure that the nerve leftovers were destroyed, the renal artery was stained with phenol 10% in ethanol 90% for 3 min. Finally, the skin and muscles were sutured, and the animal was returned to the cage following recovery (3,33) (Fig. 3B).

The estrous cycle

The estrous cycle refers to the reproductive cycle of rodents. The cycle comprises four phases, i.e., proestrus, estrus, metestrus, and diestrus, lasting between 4 - 5 days. A vaginal smear is the method typically employed to identify the estrous cycle phases. The method is reliable and accurate for the microscopic examination of vaginal cells. In this study, the vagina was washed by slowly releasing a little normal saline and then aspirating the liquid by a pipette tip. The liquid containing a few drops

of cell suspension was then positioned on a glass slide and observed under a microscope. Vaginal secretions consist of three types of cells: leukocytes, cornified epithelial cells, and nucleated epithelial cells. The estimation of the estrous cycle phase was based on the ratio of these cells in vaginal secretions. The proestrus phase is characterized by a large number of round nucleated cells with uniform appearance and size. They may appear singly or in clusters. The estrous phase is specified by an abundance of cornified anucleated epithelial cells. Metestrus contains a large number of leukocytes and a small number of large, non-granular, and anucleated cornified epithelial cells (34). Diestrus contains numerous polymorphonuclear leukocytes and a small number of cornified and epithelial cells. Consequently, we utilized female rats in the same diestrus sexual phase.

Experimental protocol

Control phase

The animals were allowed at least for 30 min to reach stable conditions as the equilibration period. RPP, RVR, MAP, and RBF values were measured as baseline data gathered during the final five min referred to as the control phase.

Saline/antagonist infusion phase

After the control phase, the MasR antagonist (A779) was injected using a micro syringe injection pump (New Era Pump System Inc., Farmingdale, USA) for 30 min. The injection of A779 (Bachem Bioscience Inc., Pennsylvania, USA) was conducted at a bolus dose of 50 µg/kg followed by a continuous infusion of 50 µg/kg/h. As a vehicle, an equal volume of normal saline 0.9% was used instead of A779. The values of RPP, RVR, MAP, and RBF were collected and analyzed at the final five min as a saline/antagonist impact.

Ang II infusion phase

After administration of A779 or vehicle, Ang II was infused over 15 min at doses of 100, 300, and 1000 ng/kg/min, whereas the injection of saline or A779 continued until the end of the experiment. The data collected over the last 3 to 5 min of each dose of Ang II were considered a vascular response to Ang II infusion. At the

end, the overdose of urethane (approximately five times the normal anesthetic dose) was injected through the left jugular vein catheter to sacrifice the rats. Then, the left kidneys were removed and immediately weighed.

Statistical analysis

Data were statistically analyzed using SPSS version 22 software and presented as mean ± SEM. The comparison of baseline data was performed using an unpaired Student's t-test. Also, the analysis of repeated measures with factors including group, treatment, and their interaction was used to examine the effects of antagonist or vehicle on baseline variables and responses to graded Ang II administration. In addition, paired Student's t-test was used to compare the weight of left and right kidneys within groups. Unpaired Student's t-test was applied to compare the weight of the right or left kidney between groups. The data of the vehicle/antagonist and the Ang II stages were presented as percentage changes. Also, the data of the control stage were represented as original data. P -value ≤ 0.05 was considered statistically significant.

RESULTS

Baseline data: renal and systemic hemodynamics

Baseline data showed that both male and female rats undergoing chronic renal sympathectomy significantly had higher RVR than rats with intact renal nerve ($P < 0.001$). Also, chronic sympathectomized male ($P = 0.001$) and female rats ($P < 0.001$) showed lower RBF than the intact groups, significantly (Fig. 4). RPP in denervated male ($P < 0.01$) and female ($P < 0.05$) rats increased significantly compared to non-denervated rats. Also, MAP increased slightly in the sympathectomy groups compared to the intact groups, although it was not statistically significant (Fig. 4).

Hemodynamic responses to antagonist/vehicle infusion

Systemic and renal hemodynamic responses in the antagonist/vehicle phase were compared between intact and chronic sympathectomized rats treated with saline or A779 in both sexes.

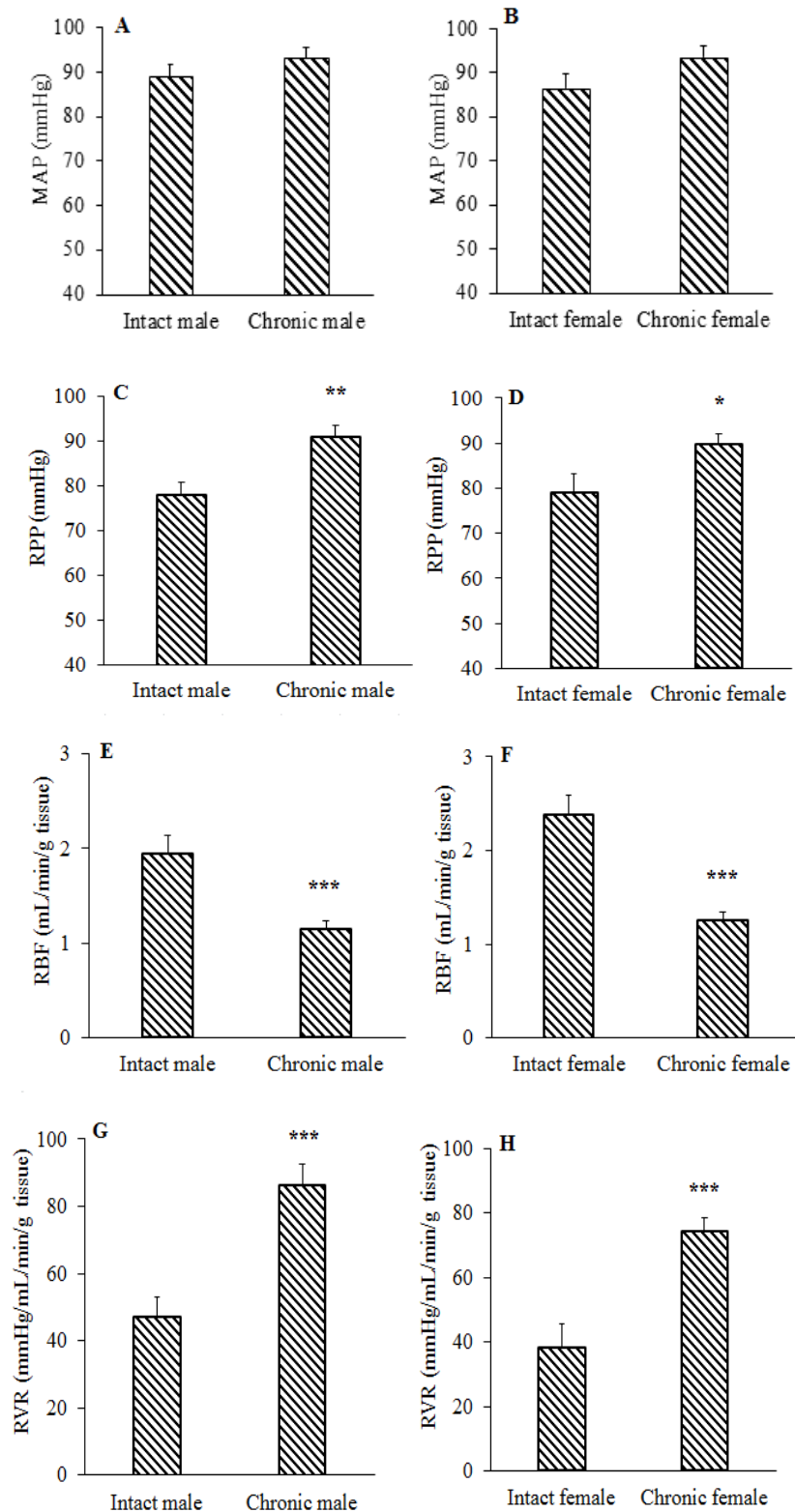


Fig. 4. Effect of chronic renal sympathectomy on the baseline systemic and renal hemodynamic data in all experimental groups. (A) Comparison of MAP between chronic (n = 14) and intact male groups (n = 11); (B) comparison of MAP between chronic (n = 13) and intact female groups (n = 10); (C and D) comparison of RPP between chronic and intact groups in each sex; (E and F) comparison of RBF/g of left kidney weight between the chronic and intact groups in each sex; (G and H) comparison of RVR/g of left kidney weight between the chronic and intact groups in each sex. Data were represented as mean ± SEM. * $P \leq 0.05$, ** $P \leq 0.01$, and *** $P \leq 0.001$ indicate significant differences in comparison with the respective intact group. MAP, Mean arterial pressure; RPP, renal perfusion pressure; RBF, renal blood flow; RVR, renal vascular resistance.

Systemic hemodynamics

MAP and RPP were not different significantly in response to saline or antagonist injection in the chronic male saline group and the chronic male A779 group compared to the intact male saline group and the intact male A779 group, respectively. Similar findings

were observed in female groups. Also, the systemic hemodynamic parameters in the saline or antagonist administration phase were not different significantly from the baseline in the mentioned groups, except that the infusion of A779 significantly reduced basal MAP and RPP only in male groups (Fig. 5).

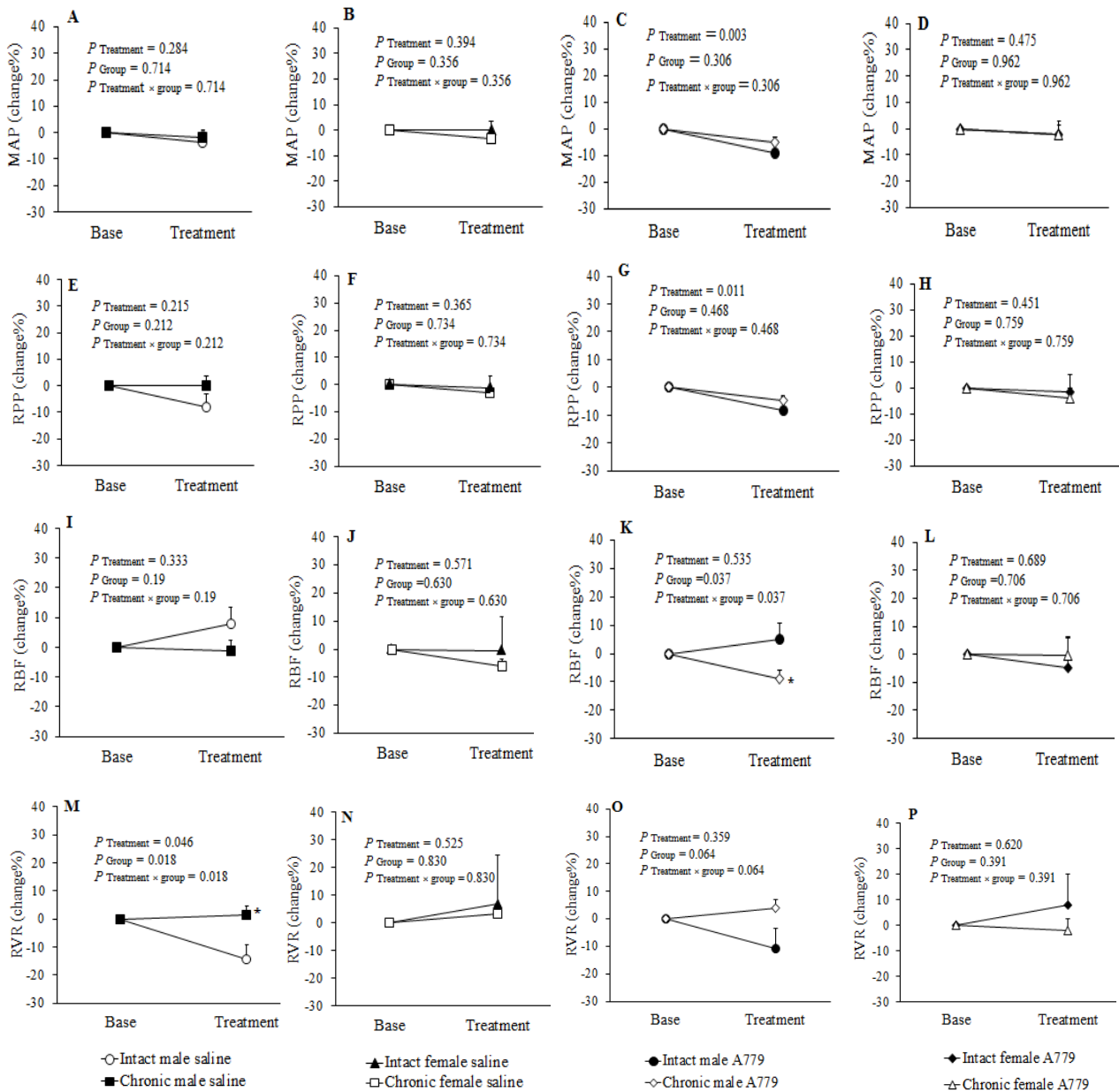


Fig. 5. Systemic and renal hemodynamic data before (base) and after (treatment) saline or antagonist infusion in all experimental groups. (A-D) Comparison of MAP between intact and chronic groups receiving saline and A779 in each sex; (E-H) comparison of RPP between intact and chronic groups receiving saline and A779 in each sex; (I-L) comparison of RBF between intact and chronic groups receiving saline and A779 in each sex; (M-P) comparison of RVR between intact and chronic groups receiving saline and A779 in each sex. Data were represented as mean \pm SEM. * $P < 0.05$ indicates significant differences in comparison with the respective intact group. MAP, Mean arterial pressure; RPP, renal perfusion pressure; RBF, renal blood flow; RVR, renal vascular resistance.

Renal hemodynamics

In the saline or antagonist injection phase, RBF did significantly not change in the chronic male saline group compared to the intact male saline group, while RBF significantly decreased in the chronic male A779 group in comparison to the intact male A779 group. On the other hand, there were no significant changes in RBF in the chronic female group compared to the intact female group receiving either saline or A779. In addition, RVR did not change in response to saline or antagonist injection in the chronic female saline and chronic female A779 groups compared to the intact female saline and intact female A779 groups, respectively. RVR significantly increased in the chronic male saline group compared to the intact male saline group, but the blockade of the Mas receptor by A779 could not significantly alter RVR in the chronic male A779 group compared to the intact male A779 group. On the other hand, in the saline or antagonist phase, RBF and RVR did not have significant changes in any groups compared to the control phase, except that RVR had a

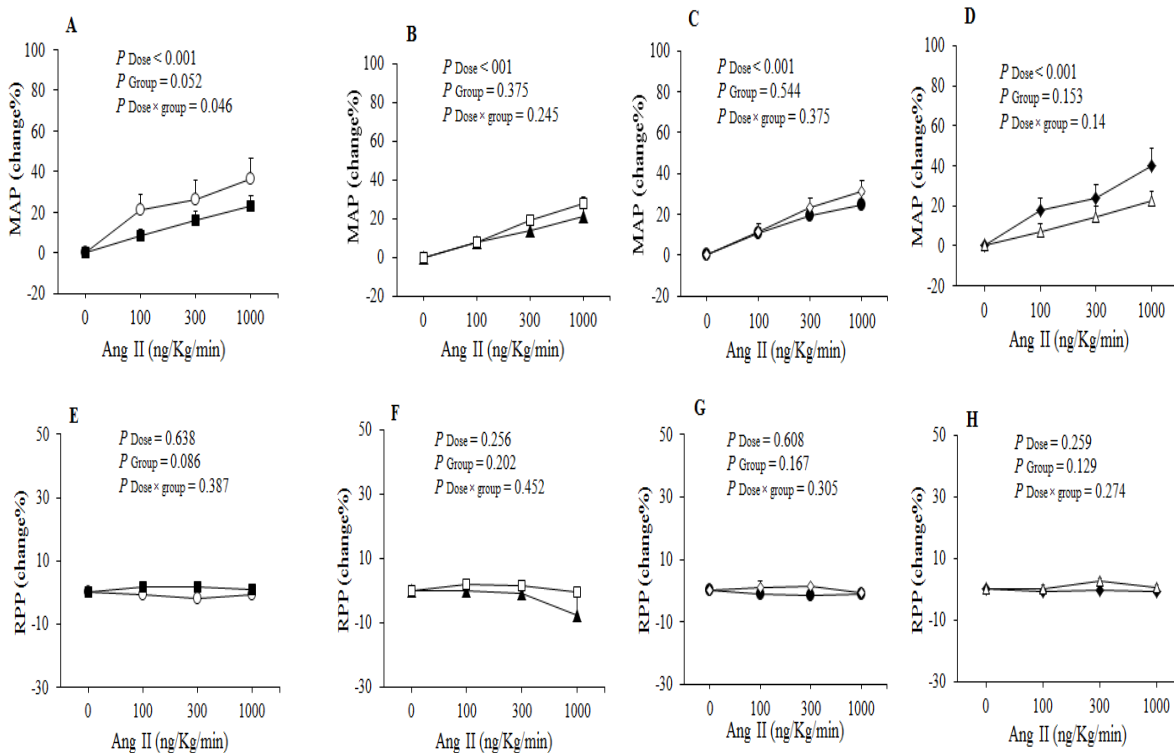
significant change in the saline phase compared to the control phase in the male groups (Fig. 5).

Hemodynamic response to Ang II infusion

Systemic and renal hemodynamic responses to Ang II administration were compared between intact and chronic sympathectomized rats treated with saline or A779 in both sexes.

Systemic hemodynamics

MAP and RPP in response to Ang II were not different significantly in the chronic male saline and chronic male A779 groups compared to the intact male saline and intact male A779 groups, respectively. In addition, MAP and RPP responses to Ang II in female rats receiving saline or antagonist were similar to male groups. On the other hand, MAP was significantly increased in response to Ang II in all experimental groups. However, RPP in response to Ang II had no significant change in all groups, because RPP was maintained by manipulating the aortic clamp during Ang II injection (Fig. 6).



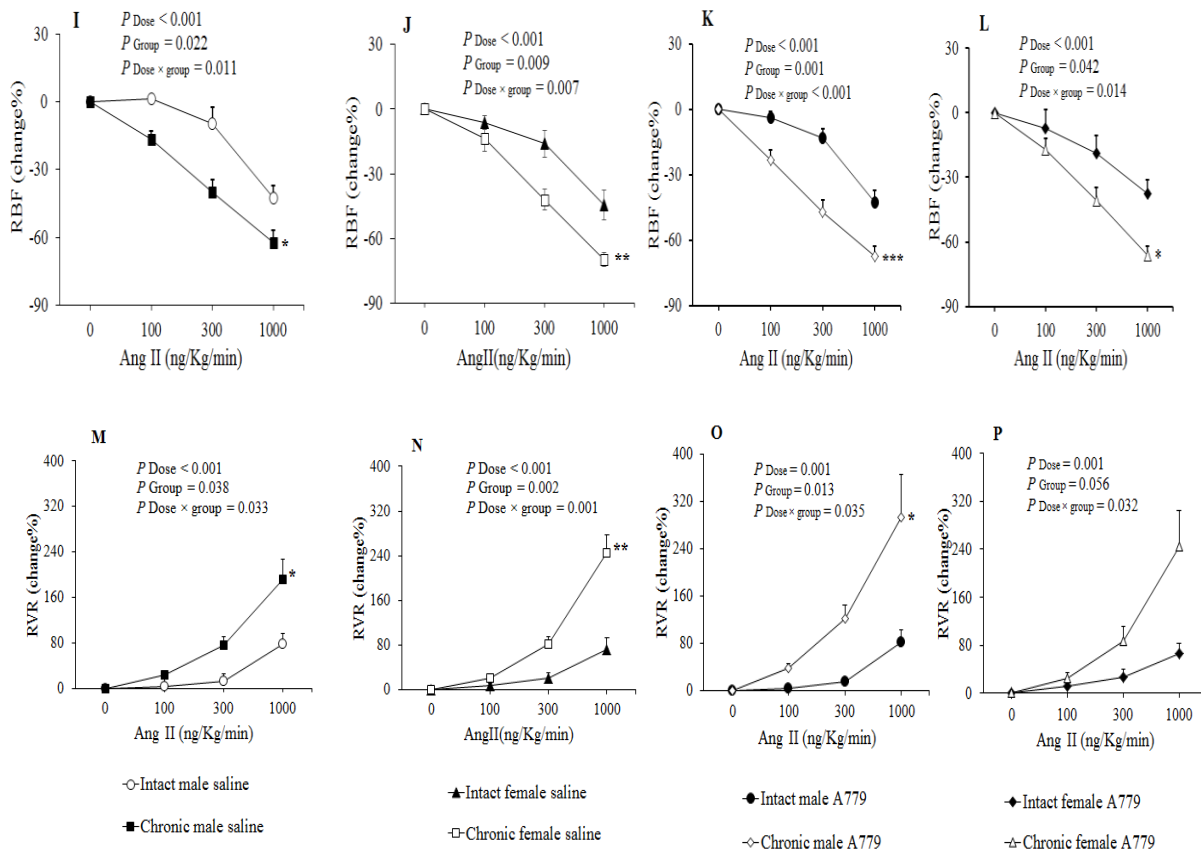


Fig. 6. Effect of infusion of different doses of Ang II on systemic and renal hemodynamic data in all experimental groups. (A-D) Comparison of MAP between intact and chronic groups receiving saline or A779 in each sex; (E-H) comparison of RPP between intact and chronic groups receiving saline or A779 in each sex; (I-L) comparison of RBF between intact and chronic groups receiving saline or A779 in each sex; (M-P) comparison of RVR between intact and chronic groups receiving saline or A779 in each sex. Data were represented as mean \pm SEM. * $P \leq 0.05$, ** $P \leq 0.01$, and *** $P \leq 0.001$ represent significant difference than intact group. MAP, Mean arterial pressure; RPP, renal perfusion pressure; RBF, renal blood flow; RVR, renal vascular resistance.

Renal hemodynamics

Sympathectomy significantly decreased RBF values higher than non-sympathectomy in response to Ang II in both male and female genders receiving saline or A779. On the other hand, the response of RVR to Ang II increased significantly in the chronic male saline group than in the intact male saline group. A significant difference also was seen between intact and sympathectomized males when the Mas receptor was blocked by A779. In addition, there was a significant increase in RVR response to Ang II in the chronic female saline group than in the intact female saline group. Although, it was not statistically significant in females receiving A779. It is noteworthy that all experimental groups had a significant decrement and a significant increment in responses of RBF and

RVR to progressive infusion of Ang II, respectively (Fig. 6).

Kidney weight

After the right nephrectomy, the weight of the left kidney increased significantly compared to the weight of the right kidney in chronic male and female groups receiving saline or A779. A similar observation was seen in intact male and female groups receiving saline or A779. The weight of the left kidney in the sympathectomized group was higher than one in the intact group in male and female rats receiving saline or A779, significantly. On the other hand, there was no significant difference in the weight of the right kidney between the chronic and the intact male groups receiving saline or A779. Also, there was a similar trend in female groups (Fig. 7).

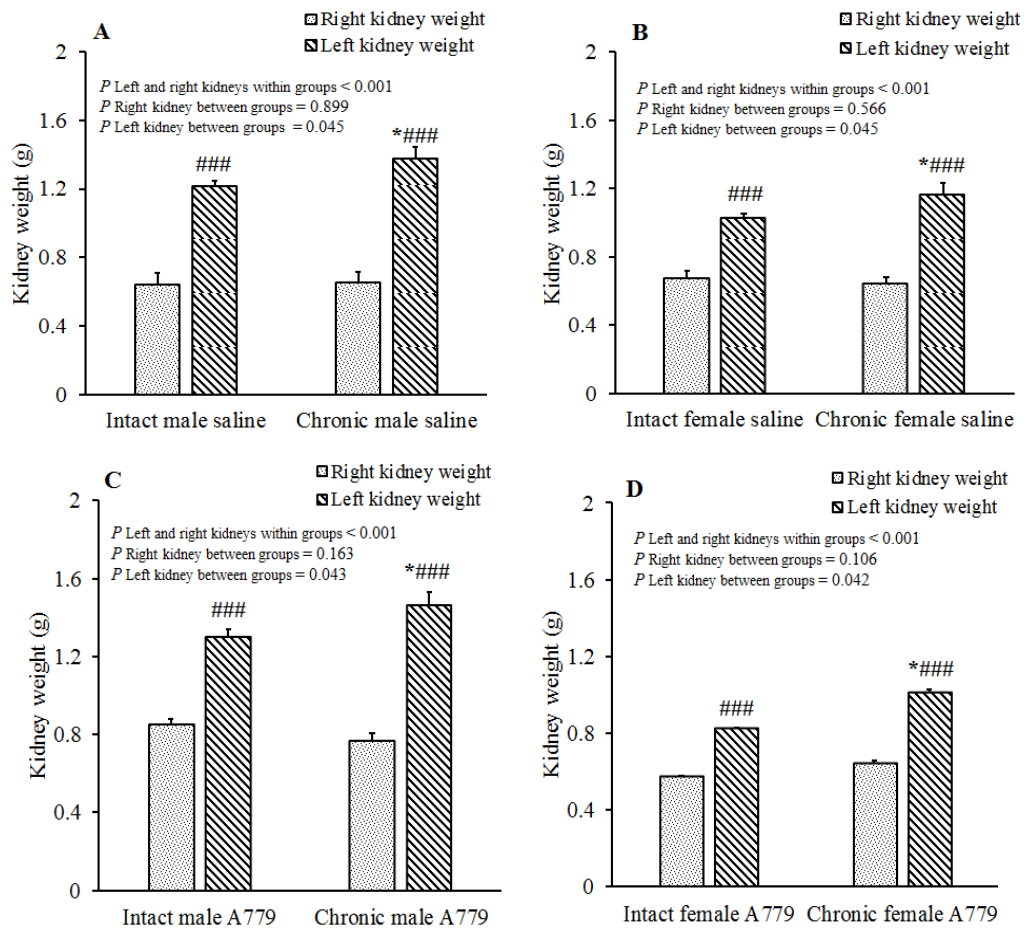


Fig. 7. The weight values of right and left kidneys in intact and chronic groups receiving saline or A779. The weight of the left kidney shows the effects of nephrectomy alone and the combination of denervation and nephrectomy in the intact and chronic groups, respectively. (A) Comparison of kidney weight values in male groups receiving saline; (B) comparison of kidney weight values in female groups receiving saline; (C) Comparison of kidney weight values in male groups receiving A779; and (D) comparison of kidney weight values in female groups receiving A779. Data were represented as mean \pm SEM. * $P \leq 0.05$ represents significant difference with the respective intact group; ### $P \leq 0.001$ versus respective right kidney weight.

DISCUSSION

The principal target of the present study was to identify the effect of chronic renal sympathectomy on renal hemodynamics under normal conditions as well as in response to Ang II in male and female rats and clear the MasR role in the responses.

The current results showed that chronic renal sympathectomy increased base RVR. There are several ways to increase resistance. First, the presence of sympathetic nerves in the blood vessel wall affects the mechanisms of flow response. The myogenic tone of rabbit ear artery smooth muscle increases 21 days after sympathetic denervation (35). The alterations such as increased internal tone, a simultaneous

decrease in flow relaxation, nonspecific sensitivity due to decreased sodium pump activity, changes in the flow sensor in the arterial wall, changes in wall composition, and endothelium-dependent mechanisms can play a role in changes after denervation (35). Due to the uncertainty surrounding the flow response mechanisms, these hypotheses have been virtually rejected (35).

Second, the increase in RVR can be caused by changes in renal artery morphology. The arterial wall of rabbits thickens six weeks after the removal of noradrenergic nerve fibers surrounding the middle cerebral artery, possibly due to the suppression of a regulatory trophic factor. The changes including increases in the number of organelles, the size of the

nucleus, the amount of extracellular connective tissue and collagen, as well as the hypertrophy of vascular smooth muscle cells can participate in the thickening (36). Studies on rabbit aorta (37) and saphenous arteries of Wistar-Kyoto rats (38) showed similar results.

Third, denervation increases oscillatory contractions (vasomotion) and sensitivity to α -adrenergic agonists in the denervated artery due to increased expression of gap junctions. A study reported that six to ten days after sympathetic denervation of the tail artery of Wistar-Kyoto rats, the expression of connexin 43 (which forms gap junctions) increased (39). Increased oscillatory activity augments vascular resistance by boosting calcium flux in the vascular smooth muscle membrane (40). In addition to increasing gap junctions (41), denervation also raises responsiveness to adrenergic agonists and vascular resistance through increasing receptor affinity (42).

Fourth, the nerves around the resistance arteries including the rat mesenteric artery contain neuropeptide Y and calcitonin gene-related peptide (CGRP). Neuropeptide Y involves in neurogenic vasoconstriction, whereas CGRP participates in neurogenic vasodilation. Therefore, depending on the fiber type, denervation by removing CGRP-containing nerves can increase vasoconstriction (43).

Finally, the increase in RVR following denervation does not appear to be a consequence of the vascular device or phenol (as a confounder). To this end, a study comparing the effects of denervation with intraperitoneal reserpine and topical phenol glycerol 5% on the smooth muscle contractions of the rat tail artery rejected this possibility (39).

The current study demonstrated that chronic renal sympathectomy increased RPP in the autoregulatory range (60 - 100 mmHg) due to increasing RVR to maintain relative GFR, RBF, and kidney function. RPP is one of the primary factors influencing RBF (44). The increase in RVR dramatically impairs renal perfusion (45). Thus, elevated perfusion pressure provides the energy necessary to overcome blood flow resistances caused by vessel diameter, red blood cell deformation, and viscosity (46) and rapidly reverses renal

hypoperfusion. RPP reflects RVR (47), and the greater the vessel resistance, the greater the increase in RPP (25). Failure to restore RBF and renal perfusion can lead to ischemic nephropathy by reducing glomerular filtration pressure (47). Therefore, when RVR rises, it is necessary to maintain an adequate level of RPP for keeping RBF within an acceptable range and protecting the kidney from insufficient blood flow (48,49).

There are several compensatory mechanisms for increasing RPP. Arterial stenosis reduces the hydrostatic pressure in the renal artery, sensed by the juxtaglomerular cells of the afferent artery. The activating of intrarenal baroreceptor mechanism causes the release of renin, which increases the local and systemic formations of Ang II (50). In addition, in response to a decrease in RBF, prostaglandin I₂ in the renal cortex can boost renin secretion (51). Then, Ang II formed by the direct vascular effects and the activation of sodium retention mechanisms increases circulating blood volume and enhances RPP and flow beyond stenosis to normal levels (25,50).

This study showed that MAP did not increase in response to increased RVR in chronic renal sympathectomy. Over time, mechanisms in the kidney appear to prevent the elevation of RPP beyond the autoregulatory range and the onset of hypertension. The kidneys serve as a long-term regulator of arterial pressure through the pressure-natriuresis mechanism, wherein an increase in RPP leads to a rise in the excretion of sodium in the presence of a sufficient number of functionally active nephrons (26,52,53).

High blood pressure occurs only when the relationship between arterial pressure and sodium excretion shifts to higher pressures (28). Pressure natriuresis mechanisms to reduce tubular reabsorption and to increase renal interstitial hydrostatic pressure are related to nitric oxide, prostaglandin E₂ and kinins, and the reduction of Ang II (27). In response to an increase in RPP, the synthesis and release of prostaglandin E₂ from the kidney increase, thereby inhibiting renal vasoconstriction (54). It also prevents the action of antidiuretic hormones in the kidney and directly inhibits sodium reabsorption in the kidney (55,56). The lack of prostaglandin production causes high

blood pressure (54). Bradykinin hormone shares similar characteristics with prostaglandin. The secretion of these substances is responsible for maintaining blood pressure at a normal level (57,58).

The greater distribution and function of the ACE2/Ang-(1-7)/MasR arm and the reduced activity of the ACE/Ang II/AT1R arm are other mechanisms that aid in maintaining normal blood pressure (59). Furthermore, the absence of renal sympathetic nerves can also prevent hypertension caused by increased RVR *via* reducing renin secretion and increasing prostaglandin-dependent diuresis and natriuresis (60-62). When the regulatory mechanisms of blood pressure fail, excessive increases in MAP and RPP lead to increase renal tissue pressure and GFR. An increase in kidney tissue pressure and GFR causes a further increase in RVR through an increase in extravascular pressure and a decrease in the transmural pressure of Bowman's capsule, respectively, which aggravate the conditions (63).

The findings of this study showed that chronic renal sympathectomy changes the renal response to Ang II administration, but not the systemic one, and the blockade or without blockade of the MasR does not affect the response. One study demonstrated that the pressor response to Ang II increases in autonomic failure; after denervation, blood vessels oversensitize to small doses of Ang II (64). There is a traditional explanation for the increasing pressor response to Ang II. The low endogenous levels of Ang II (the normal values of Ang II plasma level are 62 ± 13 fmol/mL (65) and 34.6 ± 3.2 fmol/mL (66) in non-nephrectomized rats and nephrectomized rats, respectively) lead to decreased receptor occupancy, thereby increasing receptor accessibility for administered Ang II. However, in chronic sympathectomy which is accompanied by elevated plasma renin activity due to an increase in RVR, the degree of receptor occupancy may not be significant, but the number of receptors or their nature may increase or change (67). According to Wilkes's study performed on the kidney with normal nerve activity, the number of Ang II receptors exhibits an increment of 50% in the glomeruli of denervated kidneys, seven days after RDN

(68). Also, the high activity of the renal sympathetic nerve (69) changes the expression of RAS receptors (70) and RDN results in an almost normal gene expression pattern of the receptors (70). It is not clearly known how RDN modulates the expression of AT1R and AT2R. Maybe it results from a direct effect of renal nerves on the transcription or trafficking of AT1R and AT2R (71). The cutoff of sympathetic nerves in cardiomyopathy also leads to changes in AT1R and MasR (72). It appears that renal sympathectomy can affect renal function by affecting the expression of angiotensin receptors and MasR (42).

On the other hand, it has been shown that the smooth muscle of denervated vessels has a more nonspecific sensitivity to the effects of constrictors (35), and vascular denervation can increase the amplitude of vascular oscillation in response to vasoconstrictors (39). In addition, it has been evidenced that as a result of autoregulation, an increase in RPP causes an increment in vasopressor-induced renal vasoconstriction (73).

This study also indicated that the weight of the left kidney was enhanced compared to the right kidney probably due to the compensatory hypertrophy of the kidney following right nephrectomy. This increment was greater in the sympathectomy groups than one in the intact groups, which presumably resulted from the rising of RVR. Following contralateral nephrectomy, the mass of the remaining kidney increases, mostly achieved through increasing the size of nephrons (tubular and glomerular growth), which is called compensatory hypertrophy. In addition to structural enlargement, functional adaptations also occur in the remaining nephrons, including an increase in filtration rate (74). The role of RVR in the renal compensatory hypertrophy process has been previously discussed (31). The compensatory hypertrophy of the remaining kidney is proportional to the resistance encountered. In this regard, an experiment with partial aortic constriction increased RVR in nephrectomy animals and observed greater renal hypertrophy as a compensatory response (31). Moreover, the increase in RPP when the RVR enhances, due to increasing in tissue pressure can result in a secondary progressive augmentation in kidney weight (63), and the

stimulating of kidney growth helps to boost kidney function (75).

CONCLUSION

This study demonstrated that an increase in RVR caused by RDN induces a decrease in RBF and renal perfusion, followed by an increase in RPP to maintain relative renal flow and renal function. However, these changes were unaffected by gender differences. Compensatory mechanisms and the absence of nerves could prevent an excessive increase in systemic blood pressure (hypertension) and an increase beyond the autoregulation of RPP (60 - 100 mmHg). Increased RVR also promotes compensatory hypertrophy in nephrectomized animals, contributing to improving renal function. On the other hand, the increased resistance augments the response of the renal vessels to vasopressors such as Ang II.

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Conflict of interest statement

All authors declared no conflict of interest in this study.

Authors contributions

H. Hosseini-Dastgerdi was conducted to run the experimental procedure and data collecting, involving data analysis and preparing the first draft of the manuscript. A.A. Pourshanazari designed the study, supervised the data collecting, and helped in article preparation and data analysis. M. Nematbakhsh proposed and designed the project, supervised experimental procedures and data collection, analyzed and finalized the experimental data, and edited and finalized the manuscript. The finalized article was approved by all authors.

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