Original Article

The Role of Angiotensin II Infusion on the Baroreflex Sensitivity and Renal Function in Intact and Bilateral Renal Denervation Rats

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Abstract

Background: The role of renin-angiotensin system (RAS) in communication between renal system and cardiovascular system is extremely important. Baroreflex sensitivity (BRS) index defines as heart rate (HR) alteration versus mean arterial pressure (MAP) change ratio ($\frac{\Delta HR}{\Delta MAP}$). Sympathetic nerve is arm of the baroreflexes and any change in its activity will lead to change in the BRS. The role of angiotensin II (Ang II) infusion in systemic circulation accompanied with bilateral renal denervation (RDN) on BRS index and renal function was studied. **Materials and Methods:** Seventy-two male and female Wistar rats in 12 groups were anesthetized and catheterized. The alteration of MAP and HR responses to phenylephrine infusion compared to control groups was determined in bilateral RDN rats subjected to treat with Ang II (300 or 1000 ng/kg/min) administration. **Results:** The BRS index was elevated in Ang II-treated non-RDN (normal) male rats gradually and dose dependently ($P < 0.05$), while this index was significantly different when compared with RDN male rats ($P < 0.05$). Accordingly, the BRS index was significantly lower in RDN than non-RDN male rats, and such observation was not observed in female rats. The creatinine clearance (insignificantly) and urine flow (significantly; $P < 0.05$) were decreased in both non-RDN and RDN male and female rats treated with Ang II. In RDN model, the serum nitrite levels were decreased in male and increased in female by Ang II infusion when compared with vehicle infusion. **Conclusion:** The Ang II infusion could increase the BRS index in non-RDN (normal) male rats which is significantly greater than BRS index in RDN rats.

Keywords: *Angiotensin II, baroreflex sensitivity, renal denervation*

Introduction

Renin-angiotensin system (RAS) is a hormonal system that involves in the regulation of plasma sodium concentration and vascular tone. RAS includes vasoconstrictor and vasodilator arms that the balance between these two arms is important in the hemodynamics circulation.[1-3] The role of RAS in communication between the renal and the cardiovascular systems is extremely important, and one of the homeostatic factors that interact with RAS is baroreceptor reflex sensitivity (BRS). BRS index is a quantitative index which defines as heart rate (HR) alteration versus mean arterial pressure (MAP) change ratio ($\frac{\Delta HR}{\Delta MAP}$). BRS reflects the level of baroreflex activity, vascular tone, cardiac pump, and vascular resistance.[4,5] Recently, BRS was considered as a prognostic indicator for health and disease related to cardiovascular system, such as cardiovascular risk.[5-9] The role of angiotensin II (Ang II) in the central nervous system (CNS) associated with BRS alteration was studied.[10-12] Ang II is not able to cross the blood–brain barrier, and systemic Ang II can only pass through areas without of the barrier such as circumventricular organs (CVOs). Subfornical organ is a sensory organ that belongs to CVOs, and it affects by systemic Ang II.[13,14] The role of some of the RAS components in altering BRS in the CNS can be attributed to the role of local RAS; however, these results cannot be attributed to the entire RAS system.[15,16] It seems that study is needed to determine the role peripheral RAS (Ang II) on the BRS index.[13,17,18] In addition, the RAS function and receptor expression are reported to be gender and sex hormones related.[19-22]

On the other hand, sympathetic nerve is the most important arm of the baroreflexes and any change in its activity will lead

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to a greater change in the BRS.[23-25] BRS was considered as a prognostic indicator for health and disease related to cardiovascular system, such as cardiovascular risk, neural disorders, coronary disorders, and myocardial infarction.[5,7,26] BRS is responsible for a large part of the low-frequency fluctuation in HR variability. Understanding the role of BRS and its related factors in health and disease can be useful.[6,27] Therefore, studying the BRS index is a valuable source of information regarding its clinical knowledge and application.[9,28] Accordingly, it is hypothesized that the change of Ang II level in systemic circulation accompanied with bilateral RDN may alter BRS and renal function.

Materials and Methods

Animal

Seventy-two male and female Wistar rats (218.40 ± 1.11 g, n = 36 and 196.20 ± 0.97 g, n = 36) were used. Our experimental protocol was approved by Isfahan University of Medical Sciences Ethics Committee (Code # IR. MUI. REC.1395.3.811). The animals were divided into 12 groups (6 rats in each group) as follows:

- Group 1: Male rats treated with vehicle (saline) and then received phenylephrine (Phe)
- Group 2 and 3: Male rats treated with 300 and 1000 ng/kg/min of Ang II, respectively, and then received Phe
- Group 4: Male rats subjected to renal denervation (RDN) treated with vehicle (saline) and then received Phe
- Group 5 and 6: Male rats subjected to RDN treated with 300 and 1000 ng/kg/min of Ang II, respectively, and then received Phe
- Groups 7–12: Female rats received the same regimen as Groups 1–6, respectively.

Surgical preparation and renal denervation

Animals were anesthetized with urethane (1.7 g/kg weight) (Sigma, St. Louis, USA). Trachea was cannulated for air ventilation, and the left jugular vein was catheterized with polyethylene tubing for vehicle/Ang II and Phe infusion. Furthermore, the left carotid artery was cannulated linked to a transducer cable to Quad Bridge Amp (ADINSTRUMENTS, model: ML224, S/N: 224-0265, Australia) connected to PowerLab 4/30 hardware (ADINSTRUMENTS, model: ML866, S/N: 430-0658, Australia) and LabChart software (ADINSTRUMENTS, v7.3.7, Australia) to measure systolic pressure, diastolic pressure, MAP, and HR. MAP and HR were recorded continuously during the experiment. To perform RDN, the left and right renal afferent and efferent sympathetic innervation was exposed and bilateral RDN model was done using microscope surgery.[29,30] In sham-operated groups, the left and right renal sympathetic nerves were similarly exposed and manipulated without RDN. The bladder was cannulated for urine collecting during the Ang II and Phe infusion.

Experimental protocol

Baseline measurement and responses to angiotensin II

After catheterization, the rats were allowed to stabilize for 30–45 min as equilibrium time. The baseline data (control) for MAP and HR were considered over the last 5 min of equilibrium time. Then, vehicle or Ang II (300 or 1000 ng/kg/min) was infused intravenously using micro-syringe pump (New Era Pump System Inc. Farmingdale, NY, USA) for 15 min. MAP and HR responses to vehicle or Ang II infusion were measured over the last 3–5 min of infusion, and this state called "treat" state. Vehicle or Ang II infusion was continued until Phe infusion and BRS index measurement were completed.

Phenylephrine responses

After the response to Ang II/ vehicle measurements and accompanied with Ang II or vehicle infusion, the animals were subjected to receive Phe for BRS index determination. The single bolus dose of α-adrenergic receptor agonist Phe (0.1 mg/kg body weight) was injected intravenously. MAP and HR were determined over the Phe response time. To consider the changes of MAP and HR, the peak amplitude of pressure and bradycardia responses were determined. The ratio of HR change (ΔHR) to MAP change (ΔMAP) was calculated as the BRS index. Urine sample also was collected from the beginning of vehicle/Ang II infusion until end of Phe infusion (about 20 min). Finally, blood samples were obtained via heart puncture, and the animals were sacrificed humanely. The serum and urine creatinine (Cr) levels were measured using quantitative diagnostic kits (Pars Azmoon, Iran). Furthermore, the serum nitrite level (stable nitric oxide NO metabolite) was measured using a colorimetric assay kit involves the Griess method.

Statistical analysis

The data reported as the mean ± standard error of the mean. ANOVA for repeated measure data for MAP and HR and one-way ANOVA for Cr clearance (ClCr), urine flow (UF), and serum nitrite levels were employed to compare between the groups using Tukey test as *post hoc* test. Independent Student's *t*-test also was used for comparison between the genders. $P \leq 0.05$ was considered to be statistically significant.

Results

Mean arterial pressure and heart rate measurements

The data for MAP and HR measurements in control (equilibrium time or base), treat (vehicle or Ang II infusion), and Phe administration are tabulated in Table 1. The results showed that MAP was increased significantly by Ang II infusion in non-RDN (normal) male and female rats ($P < 0.05$) when compared with vehicle infusion. However, in RDN groups, only the high dose of Ang II

Table 1: The data for mean arterial pressure and heart rate at baseline, vehicle or angiotensin II infusion (treat) and phenylephrine infusion in male and female rats in experimental groups

Group	MAP (mmHg)						HR (beats/min)					
	Baseline		Treat (vehicle/angiotensin)		Phe		Baseline		Treat (vehicle/angiotensin)		Phe	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Vehicle	102.3±1.1	101.3±1.2	101.2±1.5	101.5±2.0	157.1±4.8	153.1±2.6	370.2±14.1	408.4±10.6	370.7±14.3	405.8±9.3	230.1±14.2	320.3±7.4
AngII (300 ng/kg/min)	98.4±0.6	100.4±1.4	111.3±0.8*	111.7±2.2*	161.2±1.4	159.2±3.2	386.7±9.2	375.6±22.4	395.7±10.1	372.6±23.3	210.5±2.8	306.9±30.6
AngII (1000 ng/kg/min)	105.8±2.0	104.8±1.3	127.1±2.4*	123.4±0.8*	155.7±2.3	157.6±1.7	375.2±14.8	383.9±7.8	387.2±12.1	380.5±8.2	201.8±3.0	272.4±26.6
P_{ANOVA} for repeated measure												
Male			P_{time} <0.0001, P_{group} =0.003, $P_{group\times time}$ <0.0001						P_{time} <0.0001, P_{group} =0.775, $P_{group\times time}$ =0.028			
Female			P_{time} <0.0001, P_{group} =0.002, $P_{group\times time}$ <0.0001						P_{time} <0.0001, P_{group} =0.351, $P_{group\times time}$ =0.266			
Vehicle + RDN	98.6±1.1	93.4±1.3	97.5±1.2	94.6±1.2	144.5±1.8	146.4±3.1	334.5±3.2	365.3±16.1	336.5±3.6	367.0±17.8	330.7±5.6	282.7±10.9
AngII (300 ng/kg/min) + RDN	93.8±1.4	90.2±0.5	103.0±3.6	92.2±1.4	152.8±3.6	115.4±3.8	354.1±7.6	282.3±0.8	355.5±6.4	282.2±0.7*	346.3±7.7	238.2±4.7
AngII (1000 ng/kg/min) + RDN	98.1±0.8	90.3±1.3	115.9±2.2*	100.2±0.5*	154.6±3.3	143.4±5.5	359.3±7.1	307.6±11.65	352.5±7.3	309.5±10.7*	324.8±6.5	269.1±22.1
P_{ANOVA} for repeated measure												
Male			P_{time} <0.0001, P_{group} =0.012, $P_{group\times time}$ <0.0001						P_{time} <0.0001, P_{group} =0.135, $P_{group\times time}$ <0.0001			
Female			P_{time} <0.0001, P_{group} <0.0001, $P_{group\times time}$ <0.0001						P_{time} <0.0001, P_{group} =0.001, $P_{group\times time}$ =0.059			

*Significant difference from vehicle group (P<0.05). Statistical analysis was obtained by repeated measure data for MAP and HR. Ang II: Angiotensin II, MAP: Mean arterial pressure, HR: Heart rate, Phe: Phenylephrine, RDN: Renal denervation

infusion increased MAP significantly in male and female rats ($P < 0.05$). The results also showed that HR response to Ang II infusion was not significantly different between the groups. However, in RDN groups, HR response to Ang II was decreased significantly in female rats alone ($P < 0.05$) when compared with control group.

Baroreceptor reflex sensitivity

The results indicated that BRS increased significantly in male rats treated with Ang II (1000 ng/kg/min) compared to vehicle or Ang II (300 ng/kg/min) treated in both RDN and non-RDN (normal) animals ($P < 0.05$) [Figure 1a]. Moreover, BRS decreased significantly in RDN male rats treated with vehicle or Ang II when compared with normal rats treated in similar manner ($P < 0.05$). In female rats, the BRS increased significantly in Ang II (1000 ng/kg/min) treated compared to vehicle or Ang II (300 ng/kg/min) treated in non-RDN (normal) animals ($P < 0.05$) [Figure 1b], and such observation was not seen in RDN groups. There is also gender difference response in BRS. For example, in non-RDN (normal) rats and when Ang II (1000 ng/kg/min) was administrated, the BRS index was 6.53 ± 0.47 and 3.28 ± 0.77 beats/min/mmHg in male and female, respectively, including significant difference between genders, while it reduced significantly to 0.75 ± 0.15 and 1.22 ± 0.54 beats/min/mmHg in male and female rats, respectively, including no significant differences between the genders.

Renal function biomarkers and nitric oxide measurement

The results indicated that ClCr (insignificantly) and UF (significantly, $P < 0.005$) decreased by Ang II infusion in all RDN and non-RDN male and female rats when compared with vehicle-treated groups [Figure 2a-d]. Moreover, the serum nitrite level decreased significantly when treated with Ang II (1000 ng/kg/min) or Ang II (300 ng/kg/min) in male rats compared to vehicle in RDN models ($P < 0.05$) [Figure 2e]. The serum nitrite level increased significantly in RDN male rats treated with vehicle compared to non-RDN male rats ($P < 0.0001$) [Figure 2e]. The serum nitrite level decreased significantly in female rats treated with Ang II (300 or 1000 ng/kg/min) compared to vehicle in non-RDN model ($P < 0.05$) [Figure 2f]. The results also showed that serum nitrite level in RDN female rats treated with Ang II (300 or 1000 ng/kg/min) was more than non-RDN ($P < 0.0001$ for Ang II 300, $P = 0.02$ for Ang II 1000) [Figure 2f]. Moreover, the result showed that serum nitrite level was difference between male and female in RDN model [Figure 2e and f].

Discussion

The main findings of this study indicated that the BRS altered significantly in RDN and non-RDN male and female rats subjected to treat with Ang II. RAS is an important regulator of homeostasis and blood pressure.[31]

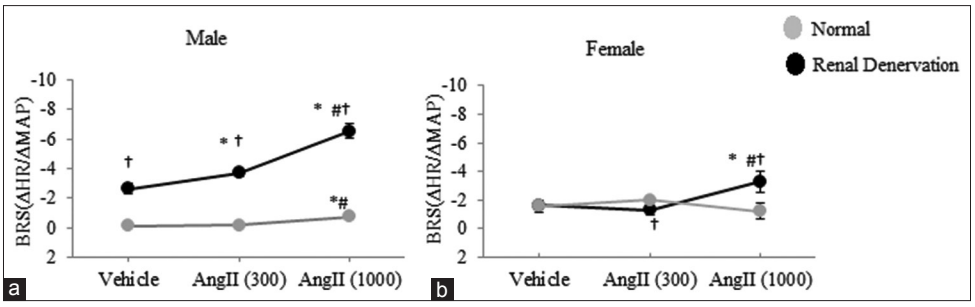

Figure 1: Data for baroreceptor reflex sensitivity in intact and renal denervation male (a) and female (b) rats in the groups treated with vehicle or two different doses of angiotensin II infusion. Ang II (300) and Ang II (1000) represent angiotensin II (30 ng/kg. min) and angiotensin II (1000 ng/kg/min). Statistical analysis was obtained by one-way ANOVA using Tukey as *post hoc*. The symbols represent significant difference from * vehicle, # Ang II (300), or †renal denervation ($P < 0.05$)

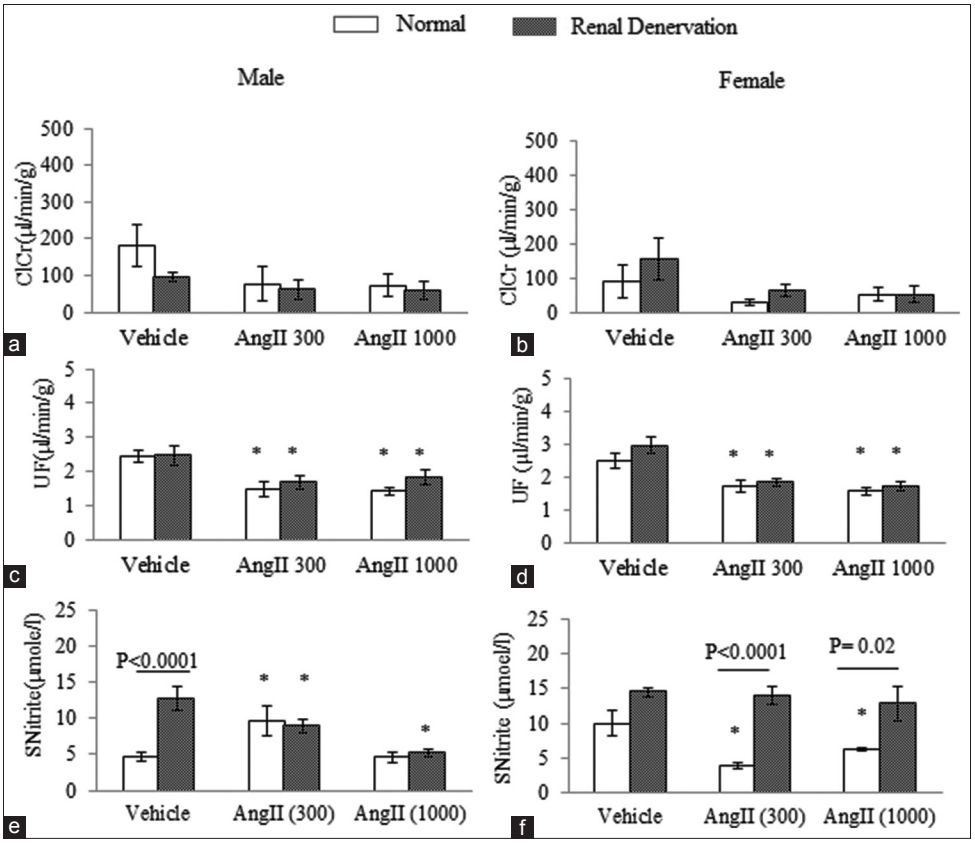

Figure 2: Data for creatinine clearance (a and b), urine flow (c and d), and serum nitrite (e and f) in intact and renal denervation male and female rats in the groups treated with vehicle or two different doses of angiotensin II infusion. Ang II (300) and Ang II (1000) represent angiotensin II (300 ng/kg/min) and angiotensin II (1000 ng/kg/min). Statistical analysis was obtained by one-way ANOVA using Tukey as *post hoc*. The star symbol (*) represents significant difference from vehicle group ($P < 0.05$)

It is reported that RAS and renal sympathetic nerves have reciprocal interaction.[30,32] Accordingly, Ang II first alters the renal sympathetic nerve activity,[33] and the renal sympathetic nerve activation second can increase RAS components expression.[34,35] The efficacy and safety of RDN in the hypertensive and nonhypertensive disorders were reported.[36] In our results, the BRS index decreased in male groups treated with vehicle and Ang II in RDN compared to non-RDN models [Figure 1a]. Sanderford *et al*. have been reported that the intravertebral infusion of Ang II can acutely attenuate the maximum renal sympathetic nerve activity.[37] Moreover, Lohmeier *et al*. reported that administration of Ang II in the CNS impaired the baroreflex control of renal sympathetic nerve activity and HR.[38] In the present finding, the BRS significantly increased by Ang II (1000 ng/kg/min) compared to Ang II (300 ng/kg/min) and vehicle-treated rats in male RDN and male and female non-RDN rats [Figure 1a and b]. It has been shown that RDN restores the baroreflex control of renal sympathetic nerve activity in renal failure Wistar-Kyoto rats.[39] Further, our study showed that the BRS significantly increased in female group treated with Ang II (300 ng/kg/min) in RDN rats compared to non-RDN model [Figure 1b]. It has also shown that the RAS acts

gender dependently in blood pressure in spontaneously hypertensive rats (SHRs).[40] Possibly, a lower sympathetic outflow to the kidney of females may contribute to their lower blood pressure.[41] Other investigations have revealed that the male SHR has increased sympathetic nerve output[42,43] and renal sympathetic nerves as a link between the long-term blood pressure and CNS are controlled by the kidneys. Hence, RDN reduces hypertension in male SHRs.[44,45] Chen and DiCarlo reported that the gain and efficiency of baroreflex control of HR in female were greater than male normotensive rats,[46] and BRS can be modulated by estrogens in normotensive rats.[47,48] Furthermore, RDN attenuates the renal nerve activity, leading to reduces central sympathetic nerve outflow.[49-51] Our results also indicated that ClCr (insignificantly) and UF (significantly) decreased by Ang II infusion in all RDN and non-RDN male and female rats when compared with vehicle-treated groups. In patients with resistant hypertension, there is a moderate-quality evidence that RDN changes major renal functions.[52,53] The result also showed that there is significant difference in serum nitrite level between RDN and non-RDN models in each of Ang II-treated female groups and vehicle-treated male groups. In line with our result, it has been shown that elevated NO signaling increases after radiofrequency RDN and plays a role in the reduction in MAP.[54] Moreover, in RDN rats, administration of L-arginine methyl ester hydrochloride has been shown that the renal effects of NO are dependent in UF, so that NO has a role of in the regulation of kidney function by modulation of renal sympathetic nerves activity.[55]

Conclusion

Ang II infusion could alter the BRS index in both RDN and non-RDN models in male and female rats. BRS index gradually and dose dependently increases in male rats treated with Ang II compared to vehicle. The greater BRS index can be indicated the gain of sensitivity of baroreceptor reflex. BRS index decreases significantly in RDN models treated with vehicle or Ang II when compared with normal rats that show RDN causing decrease of BRS, or by other words, RDN attenuates BRS response to Ang II. In fact, the RDN can restores (remodulation) of the BRS, or possibly RDN reduces the effects of the Ang II on the BRS. Disruption of the interconnection between renal sympathetic nerve and Ang II attenuates baroreflex gain that ultimately causes decreases of the BRS index. Further, there is gender difference response in BRS.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: From physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev 2007;59:251-87.
2. Unger T. The role of the renin-angiotensin system in the development of cardiovascular disease. Am J Cardiol 2002;89:3A-9A.
3. Dzau VJ. Circulating versus local renin-angiotensin system in cardiovascular homeostasis. Circulation 1988;77:I4-13.
4. La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: Measurement and clinical implications. Ann Noninvasive Electrocardiol 2008;13:191-207.
5. Conci F, Di Rienzo M, Castiglioni P. Blood pressure and heart rate variability and baroreflex sensitivity before and after brain death. J Neurol Neurosurg Psychiatry 2001;71:621-31.
6. Moak JP, Goldstein DS, Eldadah BA, Saleem A, Holmes C, Pechnik S, *et al.* Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. Heart Rhythm 2007;4:1523-9.
7. La Rovere MT, Bigger JT Jr., Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic tone and reflexes after myocardial infarction) investigators. Lancet 1998;351:478-84.
8. La Rovere MT, Maestri R, Pinna GD. Baroreflex sensitivity assessment â latest advances and strategies. European Cardiology 2011;7:89-92.
9. Mortara A, Tavazzi L. Prognostic implications of autonomic nervous system analysis in chronic heart failure: Role of heart rate variability and baroreflex sensitivity. Arch Gerontol Geriatr 1996;23:265-75.
10. Pinna GD, Maestri R, La Rovere MT. Assessment of baroreflex sensitivity from spontaneous oscillations of blood pressure and heart rate: Proven clinical value? Physiol Meas 2015;36:741-53.
11. Head GA, Saigusa T, Mayorov DN. Angiotensin and baroreflex control of the circulation. Braz J Med Biol Res 2002;35:1047-59.
12. Nautiyal M, Arnold AC, Chappell MC, Diz DI. The brain renin-angiotensin system and mitochondrial function: Influence on blood pressure and baroreflex in transgenic rat strains. Int J Hypertens 2013;2013:136028.
13. McKinley MJ, Albiston AL, Allen AM, Mathai ML, May CN, McAllen RM, *et al.* The brain renin-angiotensin system: Location and physiological roles. Int J Biochem Cell Biol 2003;35:901-18.
14. Song K, Allen AM, Paxinos G, Mendelsohn FA. Mapping of angiotensin II receptor subtype heterogeneity in rat brain. J Comp Neurol 1992;316:467-84.
15. Casto R, Phillips MI. Angiotensin II attenuates baroreflexes at nucleus tractus solitarius of rats. Am J Physiol 1986;250:R193-8.
16. Campagnole-Santos MJ, Diz DI, Ferrario CM. Baroreceptor reflex modulation by angiotensin II at the nucleus tractus solitarii. Hypertension 1988;11:I167-71.
17. Brooks VL, Ell KR, Wright RM. Pressure-independent baroreflex

resetting produced by chronic infusion of angiotensin II in rabbits. Am J Physiol 1993;265:H1275-82.
18. Wong J, Chou L, Reid IA. Role of AT1 receptors in the resetting of the baroreflex control of heart rate by angiotensin II in the rabbit. J Clin Invest 1993;91:1516-20.
19. Schneider MP, Wach PF, Durley MK, Pollock JS, Pollock DM. Sex differences in acute ANG II-mediated hemodynamic responses in mice. Am J Physiol Regul Integr Comp Physiol 2010;299:R899-906.
20. Nickenig G, Bäumer AT, Grohè C, Kahlert S, Strehlow K, Rosenkranz S, *et al.* Estrogen modulates AT1 receptor gene expression *in vitro* and *in vivo*. Circulation 1998;97:2197-201.
21. Saleh TM, Connell BJ. Role of 17beta-estradiol in the modulation of baroreflex sensitivity in male rats. Am J Physiol 1998;275:R770-8.
22. el-Mas MM, Abdel-Rahman AA. Estrogen enhances baroreflex control of heart rate in conscious ovariectomized rats. Can J Physiol Pharmacol 1998;76:381-6.
23. Epstein A, Fitzsimons J, Rolls BJ. Drinking induced by injection of angiotensin into the brain of the rat. J Physiol 1970;210:457-74.
24. Kanbar R, Oréa V, Barrès C, Julien C. Baroreflex control of renal sympathetic nerve activity during air-jet stress in rats. Am J Physiol Regul Integr Comp Physiol 2007;292:R362-7.
25. Hart EC, McBryde FD, Burchell AE, Ratcliffe LE, Stewart LQ, Baumbach A, *et al.* Translational examination of changes in baroreflex function after renal denervation in hypertensive rats and humans. Hypertension 2013;62:533-41.
26. Bär KJ, Boettger MK, Berger S, Baier V, Sauer H, Yeragani VK, *et al.* Decreased baroreflex sensitivity in acute schizophrenia. J Appl Physiol (1985) 2007;102:1051-6.
27. Faber R, Baumert M, Stepan H, Wessel N, Voss A, Walther T, *et al.* Baroreflex sensitivity, heart rate, and blood pressure variability in hypertensive pregnancy disorders. J Hum Hypertens 2004;18:707-12.
28. Routledge HC, Chowdhary S, Townend JN. Heart rate variability – A therapeutic target? J Clin Pharm Ther 2002;27:85-92.
29. Li JD, Cheng AY, Huo YL, Fan J, Zhang YP, Fang ZQ, *et al.* Bilateral renal denervation ameliorates isoproterenol-induced heart failure through downregulation of the brain renin-angiotensin system and inflammation in rat. Oxid Med Cell Longev 2016;2016:3562634.
30. Dong T, Chen JW, Tian LL, Wang LH, Jiang RD, Zhang Z, *et al.* Role of the renin-angiotensin system, renal sympathetic nerve system, and oxidative stress in chronic foot shock-induced hypertension in rats. Int J Biol Sci 2015;11:652-63.
31. Crowley SD, Coffman TM. Recent advances involving the renin-angiotensin system. Exp Cell Res 2012;318:1049-56.
32. Moretti JL, Burke SL, Davern PJ, Evans RG, Lambert GW, Head GA, *et al.* Renal sympathetic activation from long-term low-dose angiotensin II infusion in rabbits. J Hypertens 2012;30:551-60.
33. Clayton SC, Haack KK, Zucker IH. Renal denervation modulates angiotensin receptor expression in the renal cortex of rabbits with chronic heart failure. Am J Physiol Renal Physiol 2011;300:F31-9.
34. Höcherl K, Kammerl M, Kees F, Krämer BK, Grobecker HF, Kurtz A, *et al.* Role of renal nerves in stimulation of renin, COX-2, and nNOS in rat renal cortex during salt deficiency. Am J Physiol Renal Physiol 2002;282:F478-84.
35. DiBona GF. Peripheral and central interactions between the renin-angiotensin system and the renal sympathetic nerves in control of renal function. Ann N Y Acad Sci 2001;940:395-406.
36. Wang Y, Lim K, Denton KM. Editorial: Function of renal sympathetic nerves. Front Physiol 2017;8:642.
37. Sanderford MG, Bishop VS. Angiotensin II acutely attenuates range of arterial baroreflex control of renal sympathetic nerve activity. Am J Physiol Heart Circ Physiol 2000;279:H1804-12.
38. Lohmeier TE, Dwyer TM, Hildebrandt DA, Irwin ED, Rossing MA, Serdar DJ, *et al.* Influence of prolonged baroreflex activation on arterial pressure in angiotensin hypertension. Hypertension 2005;46:1194-200.
39. Khan SA, Sattar MA, Rathore HA, Abdulla MH, Ud Din Ahmad F, Ahmad A, *et al.* Renal denervation restores the baroreflex control of renal sympathetic nerve activity and heart rate in wistar-kyoto rats with cisplatin-induced renal failure. Acta Physiol (Oxf) 2014;210:690-700.
40. Reckelhoff JF, Zhang H, Srivastava K. Gender differences in development of hypertension in spontaneously hypertensive rats: Role of the renin-angiotensin system. Hypertension 2000;35:480-3.
41. Hinojosa-Laborde C, Chapa I, Lange D, Haywood JR. Gender differences in sympathetic nervous system regulation. Clin Exp Pharmacol Physiol 1999;26:122-6.
42. Friberg P, Karlsson B, Nordlander M. Autonomic control of the diurnal variation in arterial blood pressure and heart rate in spontaneously hypertensive and wistar-kyoto rats. J Hypertens 1989;7:799-807.
43. van den Buuse M. Circadian rhythms of blood pressure, heart rate, and locomotor activity in spontaneously hypertensive rats as measured with radio-telemetry. Physiol Behav 1994;55:783-7.
44. Lohmeier TE. The sympathetic nervous system and long-term blood pressure regulation. Am J Hypertens 2001;14:147S-54S.
45. Yoshida M, Yoshida E, Satoh S. Effect of renal nerve denervation on tissue catecholamine content in spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 1995;22:512-7.
46. Chen CY, DiCarlo SE. Daily exercise and gender influence arterial baroreflex regulation of heart rate and nerve activity. Am J Physiol 1996;271:H1840-8.
47. Goldman RK, Azar AS, Mulvaney JM, Hinojosa-Laborde C, Haywood JR, Brooks VL, *et al.* Baroreflex sensitivity varies during the rat estrous cycle: Role of gonadal steroids. Am J Physiol Regul Integr Comp Physiol 2009;296:R1419-26.
48. Saleh TM, Connell BJ. 17beta-estradiol modulates baroreflex sensitivity and autonomic tone of female rats. J Auton Nerv Syst 2000;80:148-61.
49. Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S, *et al.* Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. Hypertension 2010;55:619-26.
50. Barman SM, Orer HS. Rostral ventrolateral medullary but not medullary lateral tegmental field neurons mediate sympatho-sympathetic reflexes in cats. Am J Physiol Regul Integr Comp Physiol 2010;299:R1269-78.
51. Berkowitz WD, Scherlag BJ, Stein E, Damato AN. Relative roles of sympathetic and parasympathetic nervous systems in the carotid sinus reflex in dogs. Circ Res 1969;24:447-55.
52. Messerli FH, Bangalore S. Renal denervation for resistant hypertension? N Engl J Med 2014;370:1454-7.
53. Calzavacca P, Bailey M, Velkoska E, Burrell LM, Ramchandra R, Bellomo R, *et al.* Effects of renal denervation on regional hemodynamics and kidney function in experimental

hyperdynamic sepsis. Crit Care Med 2014;42:e401-9.

54. Polhemus DJ, Gao J, Scarborough AL, Trivedi R, McDonough KH, Goodchild TT, *et al*. Radiofrequency renal denervation protects the ischemic heart via inhibition of GRK2 and increased nitric oxide signaling novelty and significance. Circ Res 2016;119:470-80.
55. Harada S, Tokunaga S, Momohara M, Masaki H, Tagawa T, Imaizumi T, *et al.* Inhibition of nitric oxide formation in the nucleus tractus solitarius increases renal sympathetic nerve activity in rabbits. Circ Res 1993;72:511-6.