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Renal blood flow and vascular resistance responses to angiotensin II in irreversible and reversible unilateral ureteral obstruction rats; the role of angiotensin II type 1 and 2 receptors

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ABSTRACT

Background: Unilateral ureteral obstruction (UUO) alters the expression of renin-angiotensin system (RAS) components and angiotensin II (Ang II) as the main arm of RAS is affected by UUO.

Objectives: In this study the role of Ang II subtypes 1 and 2 receptors (AT1R and AT2R) antagonists (losartan and PD123319) was examined in renal hemodynamic responses to graded Ang II infusion in sham, 3-day UUO and removal UUO (RUUO) models in rats.

Materials and Methods: Seventy-one male Wistar rats randomly divided into three different sets of animal models; sham-operated, UUO and RUUO that each set contains three groups treated with vehicle, losartan, and PD123319. Renal vascular responses to Ang II infusion were measured at controlled renal perfusion pressure (RPP).

Results: The graded Ang II infusion decreased renal blood flow (RBF), increased renal vascular resistance (RVR) and mean arterial pressure (MAP) in vehicle or PD123319 treated groups significantly ($P<0.005$), but no significant difference was found between these treated groups. However, RBF, RVR and MAP responses to graded Ang II infusion in losartan-treated rats were attenuated significantly when compared with vehicle or PD123319 treated groups ($P<0.05$). In addition, the RBF, RVR and MAP responses to Ang II were not similar in sham, UUO and RUUO rats treated with losartan.

Conclusions: Vascular responses to Ang II in UUO and RUUO rat model treated with losartan is not as the normal pattern.

Implication for health policy/practice/research/medical education:
The expression of renin-angiotensin system (RAS) components alters in UUO model and AngII as the main arm of RAS is affected by unilateral ureteral obstruction (UUO). From the findings of the present study, we can conclude that the vascular responses to Ang II in losartan treated rats are not as the normal pattern in both UUO and removal UUO (RUUO) models.

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Original Article

1. Background

Unilateral ureteral obstruction (UUO) is an important model of progressive renal disease characterized by renal hemodynamic impairment (1). Functional and hemodynamic impairments (1,2) are associated with elevated pressure in the renal glomeruli, tubules, and ureter that can lead to histopathological (1) and morphological changes in the kidney with UUO (3). UUO decreases the renal blood flow (RBF) and increases the renal vascular resistance (RVR) (4) progressively in ipsilateral kidney until the UUO is removed, while UUO removal (RUUO) can prevent the complications of acute UUO (5). Renin-

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angiotensin system (RAS) is one of the main systems that is activated in UUO condition, and local RAS activation leads to the excessive elevation of intrarenal angiotensin II (Ang II) content (6) and induces inflammation and fibrosis in kidney suffering from UUO (7). Moreover, UUO induces podocyte injury in renal bowman's capsule and then plasma angiotensinogen is filtered within the kidney and converted to Ang II (8). This mechanism is a new pathway for local renal Ang II generation (9). Ang II alters the hemodynamic parameters in the ipsilateral kidney after UUO and can induce injury via constriction of afferent and efferent kidney arterioles (10,11). Ang II as the main bioactive product of the RAS (12), acts via Ang II receptors subtypes 1 (AT_1R) and subtypes 2 (AT_2R) (13). The most effects of Ang II are done via AT_1R in adult mammals (14). Therefore, the main classical Ang II functions such as activation of fibroblasts, inflammation, and oxidative stress are mediated by AT_1R (14,15). Studies have shown that AT_1R antagonists have a renoprotection effect and attenuate the interstitial fibrosis and apoptosis in the kidney with UUO (16,17). Ang II via AT_2R induces diuresis, natriuresis, vasodilatation, and antiproliferative responses (15). Moreover, it is reported that AT_2R antagonist (PD123319) increases the renal interstitial collagen accumulation after UUO (18). Also, it has been seen that interstitial fibrosis increases in the AT_2R knockout UUO mice (19). Renal hemodynamic responses to Ang II may act differently during UUO and after removal UUO (RUUO).

2. Objectives

The main purpose of this study was to evaluate the role of AT_1R and AT_2R antagonists on renal vascular responses to graded Ang II infusion after both UUO and RUUO in male rats.

3. Materials and Methods

3.1. Animals

Male Wistar rats (215 ± 10 g) obtained from Water and Electrolyte Research Center Animal House, Isfahan, Iran. The animals were housed at 23–25°C with a 12-hour light/dark cycle and allowed 1 week to acclimatize to this situation. The rats were fed with rat chow and had free access to tap water.

3.2. Induction of UUO and RUUO models

Rats were anesthetized with chloral hydrate (450 mg/kg, I.P., Sigma St. Louis USA) (20) and surgery was performed through an incision on left quadrant of the abdomen and the left ureter was exposed and ligated by 4-0 nylon suture to induce UUO induction (groups 4-9). A similar procedure was applied in sham groups except for UUO induction (group 1-3). But in groups 7-9 (RUUO), UUO was removed under anesthesia after three days and allowed to recover for 24 hours. In summary, the following groups were designed (n=7-10 in each group).

Groups 1-3 (named sham); sham-operated groups that treated with vehicle (group 1), losartan (group 2) and PD123319 (group 3), and then they were subjected to receive graded Ang II infusion (21).

Groups 4-6 (named UUO); UUO groups that treated with vehicle (group 4), losartan (group 5) and PD123319 (group 6), and then they were subjected to receive graded Ang II infusion.

Groups 7-9 (named RUUO); RUUO groups that treated with vehicle (group 7), losartan (group 8) and PD123319 (group 9), and then they were subjected to receive graded Ang II infusion.

3.3. Surgical preparation

Rats were anesthetized with 1.7 $g.kg^{-1}$ bodyweight urethane (Sigma St. Louis USA). The trachea was exposed and the air ventilation tube inserted to facilitate breathing. The left jugular vein was isolated, ligated distally, and cannulated with polyethylene tubing (PE 9658, Microtube Extrusions, North Rocks NSW, Australia) for vehicle/antagonist or Ang II administration. Catheters were also implanted into the left carotid and femoral arteries and then connected to a pressure transducer and a bridge amplifier (Scientific Concepts, Vic., Melbourne, Australia) for measuring mean arterial pressure (MAP) and renal perfusion pressure (RPP), respectively. The left kidney was exposed, placed and fixed in special kidney cup. Renal artery was separated from the renal vein then an ultrasound flow probe interfaced with a compatible flow meter (T108; Transonic Systems) was placed around the renal artery for RBF measuring. An adjustable clamp was placed around the abdominal aorta (above renal arteries) to maintain RPP in base levels during Ang II infusion. MAP, RPP, and RBF were monitored continuously during the experiment.

3.4. Experimental protocol

3.4.1. Baseline measurement and antagonist response

The animals were allowed to stabilize for 30-45 minutes as equilibrium time for baseline measurement. The baseline data for the MAP, RPP and RBF were obtained over the last 5 minutes of equilibrium time. Based on groups specified the animals were subjected to received either vehicle (saline), AT_1R antagonist; losartan (Merck & Co. Inc., Rathway, NJ, USA), or AT2R antagonist;

PD123319 (Sigma, St. Louis, MO, USA). Losartan and PD123319 dissolved in 0.9% w/v saline were administered as bolus doses of 5 mg kg^{-1} and 1 mg kg^{-1} followed by continuous infusions of 5 mg $kg^{-1}h^{-1}$ and 1 mg kg^{-1} h^{-1} respectively using a microsyringe infusion pump (New Era Pump System Inc., Farmingdale, NY, USA) during the experiment. The dose of losartan and PD123319 were selected based on previous studies (22, 23), while Macari et al (24) reported that PD123319 had a high affinity for AT_2R at doses less than 1000 μg/kg/min. Thirty minutes post vehicle or antagonists infusion were considered as antagonist's effect time for the measurement. MAP, RPP, and RBF were determined over the last 5 minutes period of antagonists' effect time. MAP/RBF also was calculated as RVR.

3.4.2. Response to graded Ang II infusion

Ang II was administrated intravenously 30 minutes after antagonist or vehicle started. Graded Ang II infusion (30, 100, 300, and 1000 ng kg^{-1} min^{-1}) was commenced using microsyringe pump. Each dose of Ang II was infused for a 15-minute period while RPP was maintained at pre-Ang II infusion levels by manipulation of the aortic clamp. MAP, RPP, and RBF responses to graded Ang II infusion were determined over the final 5 minutes of each infusion. At the end of the study, the animals were sacrificed humanely via an overdose of anesthetic, and the wet weight of left kidney was determined.

3.5. Ethical issues

The research was approved by Ethics Committee of Isfahan University of Medical. Prior to the experiment, the protocols were confirmed to be in accordance with the guidelines of Animal Ethics Committee of Isfahan University of Medical Sciences (code# IR.MUI.REC.1395.3.353).

3.6. Statistical analysis

The data were expressed as mean ± SEM and analysis were performed using SPSS version 20 software. The baseline data and the effect of vehicle/antagonist were analyzed by the one-way analysis of variance (ANOVA). Inter and between groups comparisons were followed by least significant difference (LSD) test. A repeated measure ANOVA was applied to compare the effect of each treatment response to Ang II. Significant differences were considered with values of $P \leq 0.05$.

4. Results

4.1. Baseline measurements

No significant differences were detected in terms of MAP, RBF, RPP, and RVR between the groups in each set of animal models (sham, UUO, and RUUO) in control or equilibrium period before infusion of vehicle or antagonists (Figure 1: A-L).

4.2. Effect of vehicle or antagonists

The results showed that vehicle (saline) infusion had no significant effect on the MAP, RPP, RBF, and RVR between the groups in each set of animal models (sham, UUO, and RUUO) 30 min post vehicle infusion (Figure 1; A-L). However, in sham-operated, UUO and RUUO models, AT_1R antagonist, losartan compared to vehicle or PD123319 decreased MAP, ($P \leq 0.004$, Figure 1: A, E and I), RPP ($P \leq 0.002$, Figure 1: F and J), and RVR ($P \leq 0.0001$, Figure 1: L) significantly, but in RUUO compared to sham-operated model, RBF was increased significantly ($P < 0.05$) by losartan, and such observation was not detected in UUO model.

4.3. Response to graded Ang II infusion

The intravenous graded Ang II infusion increased the percentage changes of MAP and RVR and decreased RBF significantly in vehicle or PD123319 treated rats in sham, UUO and RUUO models ($P < 0.05$), but no significant difference was observed between antagonists treated groups in each model. However, MAP (P dose ≤0.0001, Figure 2: A, E and I), RBF (P dose≤0.0001, Figure 2: C, G and K) and RVR (P dose ≤0.0001, Figure 2: D, H and L) were attenuated in losartan-treated groups when compared with the other groups in each models. For example; Ang II with the dose of 1000 ng kg^{-1} min^{-1} increased RBF percentage changes to 11.05% ± 6.3, -20.4% ± 8.4, 13.01 ± 5.04 respectively in sham, UUO and RUUO rats treated with losartan.

5. Discussion

The main findings indicated that RBF response to graded Ang II infusion in sham-losartan treated rats was significantly different from UUO and RUUO animal treated with losartan. Evidences have demonstrated that after UUO, local RAS strongly activates and leads to a prominent elevation of Ang II in ipsilateral kidney (25,26). Ang II via AT_1R also contributes to kidney injury (15). The previous report has shown that RVR increased and RBF decreased progressively in ipsilateral kidney suffering from UUO (27). In line with these results, in our study, 3-day UUO was associated with a significant reduction in RBF and a significant increase in RVR in the ipsilateral kidney (Figure 1). It is shown that losartan directly binds to AT_1R (28) and reduces the vasoconstriction response in kidney (27,29).

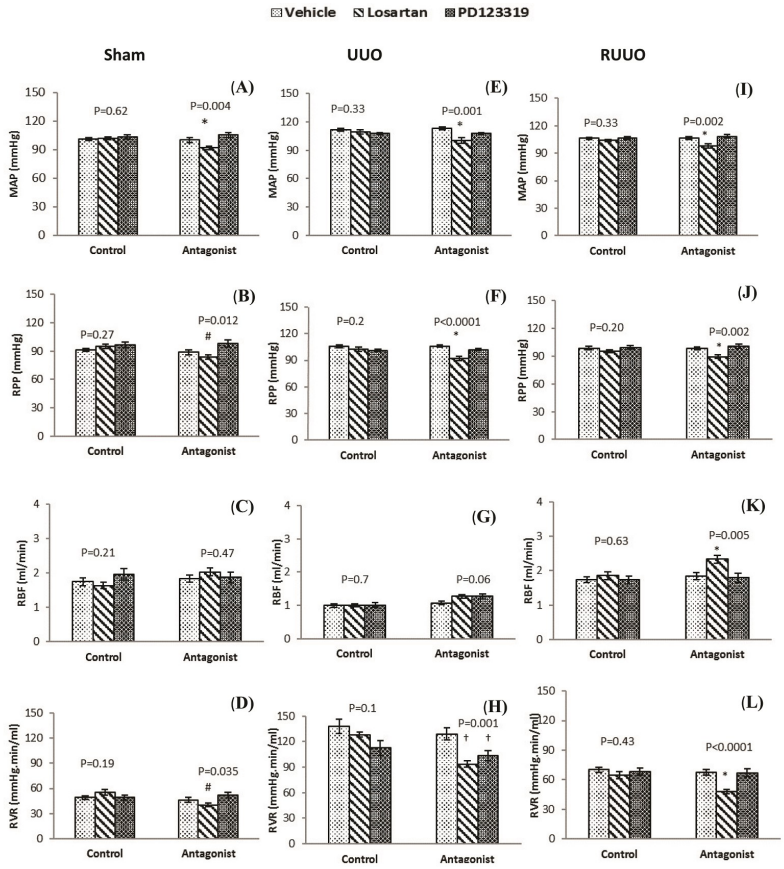

Figure 1. The hemodynamic parameters before and after administration of vehicle/antagonists in rat models (Sham, UUO or RUUO). Data are presented as mean ± SEM. The *P* values were derived from one-way ANOVA. Specific contrasts were generated by LSD test comparisons. *; Represents significant difference from the vehicle or PD123319 ($P \leq 0.05$). #; Represents significant difference from PD123319 ($P \leq 0.05$). †; Represents significant difference from vehicle ($P \leq 0.05$). n = 8–10 per group. UUO; Unilateral ureteral obstruction, RUUO: UUO removal, MAP; mean arterial pressure, RPP; renal perfusion pressure, RBF; renal blood flow, RVR; renal vascular resistance.

Furthermore, losartan improves the renal architecture, and it has renoprotective effects against tubulointerstitial fibrosis, renal ischemia and hypoxia, and oxidative stress (29,30). Our study showed that losartan decreased RVR, and also increased RBF in UUO and RUUO rats significantly (Figure 1). In concordant with our result, it has been shown that continuous injection of losartan can block the AT_1R mediated effects in the ipsilateral kidney in pigs with UUO (27). This study also supports the idea that Ang II is the main vasoconstrictor mediator that involved in hemodynamic disorder resulting from UUO (27). MAP, RVR and RBF responses to graded Ang II infusion in the losartan-treated group were significantly different from PD123319 or vehicle-treated rats in sham, UUO and RUUO models (Figure 2). Studies have confirmed a significant rise in local Ang II content, angiotensin converting enzyme, renin, and AT_1R expression in the ipsilateral kidney with prolonged UUO (29,31,32). Furthermore, Hammad et al (33) confirmed that the proportion and/or affinity of AT_1R / was increased in UUO kidney. Therefore, based on these studies, it can be concluded that AT_1R overexpression, and its functional effects, possibly alter the responses. Also, it has been found that after UUO, mechanical strain can up-regulate the AT_1R expression in podocytes; leads to podocyte injury, and then increases the local Ang II production (34). Also, it has been proved that Ang II stimulates releasing and activation of the endothelin-1 (35), while endothelin-1 has a crosstalk with Ang II in UUO (36) which mediates some of its vasoconstriction effects (37). Ang II also stimulates the release of noradrenaline from renal sympathetic nerve terminals dose dependently (38), and noradrenaline exacerbates the renal vasoconstriction (31). Together, it is suggested that Ang II may cause vasoconstriction through other mechanisms not directly related to AT_1R. To consider the renal vascular response in RUUO model, Ito et al (39) have demonstrated that, in 3-day UUO model, RBF returned to normal at 14 days after RUUO. Moreover, even short-term UUO is followed by progressive kidney

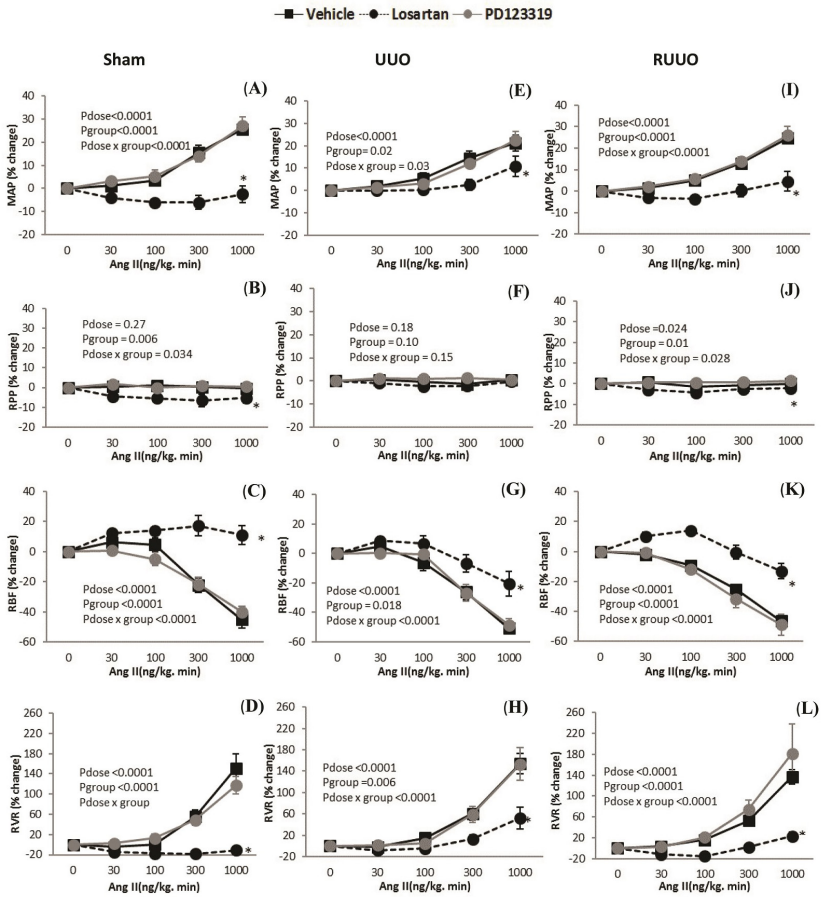

Figure 2. The percentage changes of the MAP, RPP, RBF and RVR in vehicle or losartan or PD123319 administration rats' responses to graded Ang II infusion in sham or UUO or RUUO models. Data are shown as mean ± SEM of percentage changes from baseline. The *P* values were derived from repeated measure ANOVA. ∗; Represents significant difference from the vehicle or PD123319 (P dose < 0.05). n = 8–10 per group. UUO; Unilateral ureteral obstruction, RUUO: UUO removal, MAP: Mean arterial pressure, RPP: Renal perfusion pressure, RBF; Renal blood flow, RVR: Renal vascular resistance.

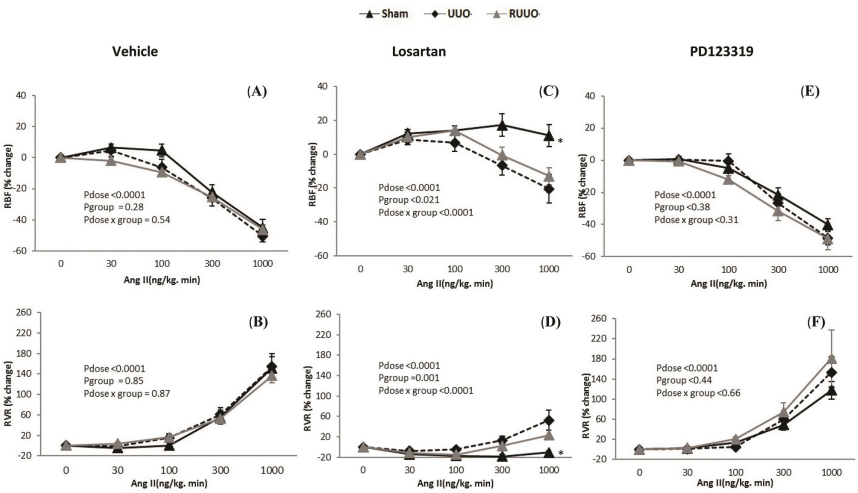

Figure 3. Effects of the vehicle (left panels) or losartan (midst panels) or PD123319 (right panels) on RBF and RVR percentage changes responses to graded Ang II infusion in sham, UUO, and RUUO rats. Data are presented as mean ± SEM. UUO: Unilateral ureteral obstruction, RUUO; UUO removal, RBF: Renal blood flow, RVR; Renal vascular resistance. *P* values were derived from repeated measure ANOVA. ∗; Represents significant difference from the vehicle or PD123319 (P < 0.05).

injury and its harmful side effect remains after RUUO (39). Our study also indicated that RBF and RVR responses to PD123319 infusion in UUO model were different with other PD123319 administrated groups (Figure 1). It is well-known that AT_2R mRNA expression and its antifibrotic effect were decreased in the kidney with UUO (40, 41), while AT_2R function and its vascular effect are against AT_1R (42). Moreover, PD123319 can interact with AT1/Mas receptors in the absence of AT_2R (43, 44). Perhaps PD123319 acts via another mechanism due to decreased AT_2R functional response in this model. PD123319 didn't alter the hemodynamic parameter in response to Ang II significantly (Figure 3). The possible reason could be related to overexpression of AT_1R, because it is documented that the renal AT_2R affinity for binding to Ang II is similar to AT_1R (45) but Ang II binding sites for AT_2R is one-fifth less than AT_1R (45).

6. Conclusions

It is concluded that both AT_1R and AT_2R are affected by 3-day UUO, but the regulatory role of AT_1R on renal hemodynamic parameters was greater than AT_2R. Also, paradoxical renal hemodynamic (RBF, RVR) responses to graded Ang II infusion in UUO or RUUO rats treated with losartan compared to sham-losartan rats were observed. This finding suggests that Ang II can cause vasoconstriction independent to direct AT_1R stimulation. Moreover, possibly the AT_1R expression is increased by UUO. However, the inhibition of AT_1R may be considered as therapeutic interventions on renal hemodynamic parameters in UUO or RUUO conditions.

Authors' contribution

JH and MM conducted the experimental procedures and helped to prepare the first draft of the manuscript. MN; designed, supervised and analyzed the research and completed the manuscript. All authors read and signed the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Vaughan ED, Marion D, Poppas DP, Felsen D. Pathophysiology of unilateral ureteral obstruction: studies from Charlottesville to New York. J Urol. 2004 Dec; 6 (172):2563-9. doi: 10.1097/01.ju.0000144286.53562.95.
2. Brenner BM, Rector FC, Barry MB. Brenner & Rector's the kidney/Brenner and Rector's the kidneyKidney. Saunders Els. 2008 Dec; 1416031057. ISBN: 1416031057.
3. Goldman L, Schafer AI. Goldman's Cecil medicine. Els Health Sci. 2011 Sep; ISBN: 9780323322850.
4. Thoeny HC, Kessler TM, Simon-Zoula S, De Keyzer F, Mohaupt M, Studer UE, et al. Renal Oxygenation Changes during Acute Unilateral Ureteral Obstruction: Assessment with Blood Oxygen Level–Dependent MR Imaging—Initial Experience 1. Radiology. 2008;247(3):754-61. doi: 10.1148/radiol.2473070877.
5. Tavukçu HH, Tinay İ, Tarcan T. To save or not to save the kidney: relieving unilateral obstruction may significantly improve an initially low split renal creatinine clearance. J Urol Surg. 2016; 1:7-12. doi: 10.4274/jus.2015.613.
6. Frokiaer J. Pharmacologic intervention in urinary tract obstruction—Is it possible? Kidney Int. 2005;68(2):894-5. doi: 10.1111/j.1523-1755.2005.00474.
7. Podhorska-Okolow M, Dzlegiel P, Gomulkiewicz A, Kisiela D, Dolinska-Krajewska B, Jethon Z, et al. Exercise-induced apoptosis in rat kidney is mediated by both angiotensin II AT1 and AT2 receptors. Histol Histopathol. 2006;21(5):459-66. doi: 10.14670/HH-21.459.
8. Matsusaka T, Niimura F, Pastan I, Shintani A, Nishiyama A, Ichikawa I. Podocyte injury enhances filtration of liver-derived angiotensinogen and renal angiotensin II generation. Kidney Int. 2014;85(5):1068-77. doi: 10.1038/ki.2013.453.
9. Matsusaka T, Niimura F, Shimizu A, Pastan I, Saito A, Kobori H, et al. Liver angiotensinogen is the primary source of renal angiotensin II. J Am Soc Nephrol. 2012; 23(7):1181-9. doi: 10.1681/ASN.2011121159.
10. Jensen AM, Li C, Praetorius HA, Nørregaard R, Frische S, Knepper MA, et al. Angiotensin II mediates downregulation of aquaporin water channels and key renal sodium transporters in response to urinary tract obstruction. Am J Physiol Renal Physiol. 2006;291(5):F1021-32. doi: 10.1152/ajprenal.00387.
11. Shin G-T, Kim W-H, Yim H, Kim M-S, Kim H. Effects of suppressing intrarenal angiotensinogen on renal transforming growth factor-β1 expression in acute ureteral obstruction. Kidney Int. 2005;67(3):897-908. doi: 10.1111/j.1523-1755.2005.00154.
12. Paul M, Mehr AP, Kreutz R. Physiology of local renin-angiotensin systems. Physiol Rev. 2006;86(3):747-803. doi: 10.1152/physrev.00036.2005.
13. Touyz RM, Schiffrin EL. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells.

Pharmacol Rev. 2000;52(4):639-72.
14. Radović N, Aralica G, Galesić Ljubanović D, Jelec V, Kontek M. Effect of unilateral ureteral obstruction and anti-angiotensin II treatment on renal tubule cell apoptosis and interstitial fibrosis in rats. Croat Med J. 2008;49(5):600–7. doi: 10.3325/cmj.2008.5.600.
15. Esteban V, Lorenzo O, Rupérez M, Suzuki Y, Mezzano S, Blanco J, et al. Angiotensin II, via AT1 and AT2 receptors and NF-κB pathway, regulates the inflammatory response in unilateral ureteral obstruction. J Am Soc Nephrol. 2004;15(6):1514-29. doi: 10.1097/01.ASN.0000130564.75008.
16. Wamsley-Davis A, Padda R, Truong LD, Tsao CC, Zhang P, Sheikh-Hamad D. AT1A-mediated activation of kidney JNK1 and SMAD2 in obstructive uropathy: preservation of kidney tissue mass using candesartan. Am J Physiol Renal Physiol. 2004;287(3):F474-80. doi: 10.1152/ajprenal.00452.2003.
17. Perico N, Benigni A, Remuzzi G. Present and future drug treatments for chronic kidney diseases: evolving targets in renoprotection. Nat Rev Drug Discov. 2008;7(11):936-53. doi: 10.1038/nrd2685.
18. Satoh M, Kashihara N, Yamasaki Y, Maruyama K, Okamoto K, Maeshima Y, et al. Renal interstitial fibrosis is reduced in angiotensin II type 1a receptor-deficient mice. J Am Soc Nephrol. 2001;12(2):317-25.
19. Ma J, Nishimura H, Fogo A, Kon V, Inagami T, Ichikawa I. Accelerated fibrosis and collagen deposition develop in the renal interstitium of angiotensin type 2 receptor null mutant mice during ureteral obstruction Rapid Communication. Kidney Int. 1998;53(4):937-44. doi: 10.1111/j.1523-1755.1998.00893.
20. Dehghani A, Saberi S, Nematbakhsh M. Nitric Oxide Synthases Blockade; L-NAME and Estradiol Alter Renal Blood Flow Response to Angiotensin 1-7 in Ovariectomized Rats. Indian J Physiol Pharmacol. 2015; 59(3):266-74.
21. Nematbakhsh M, Safari T. Role of angiotensin type 2 receptor on nitric oxide production response to angiotensin II administration in ovariectomised rats treated with estradiol. Int J Prev Med. 2014;5(2):238–240.
22. Mansoori A, Oryan S, Nematbakhsh M. Role of Mas receptor antagonist (A779) on pressure diuresis and natriuresis and renal blood flow in the absence of angiotensin II receptors type 1 and 2 in female and male rats. J Physiol Pharmacol. 2014;65(5):633-9.
23. Hilliard LM, Nematbakhsh M, Kett MM, Teichman E, Sampson AK, Widdop RE, et al. Gender differences in pressure-natriuresis and renal autoregulation. Hypertension. 2011;57(2):275-82. doi: 10.1161/HYPERTENSIONAHA.110.166827.
24. Macari D, Bottari S, Whitebread S, De Gasparo M, Levens N. Renal actions of the selective angiotensin AT2 receptor ligands CGP 42112B and PD 123319 in the sodium-depleted rat. Eur J Pharmacol. 1993;249(1):85-93. doi:10.1016/0014-2999(93)90665-5.
25. Chevalier RL. Obstructive nephropathy: towards biomarker discovery and gene therapy. Nat Clin Pract Nephrol. 2006;2(3):157-68. doi: 10.1038/ncpneph0098.
26. Uchida Y, Miyajima A, Kikuchi E, Kozakai N, Kosaka T, Ieda M, et al. Renal damage inhibited in mice lacking angiotensinogen gene subjected to unilateral ureteral obstruction. Urology. 2009;74(4):938-43. doi: 10.1016/j.urology.2009.02.059.
27. Hvistendahl JJ, Pedersen TS, Djurhuus JC, Pedersen EB, Frøkiær J. Losartan attenuates renal vasoconstriction in response to acute unilateral ureteral occlusion in pigs. Urol Res. 2002;30(3):169-77. doi: 10.1007/s00240-002-0240.
28. Zou L-X, Imig JD, Hymel A, Navar LG. Renal uptake of circulating angiotensin II in Val5-angiotensin II infused rats is mediated by AT1 receptor. Am J Hypertens. 1998;11(5):570-8. doi: 10.1016/S0895-7061(97)00410.
29. Soliman SA, Shokeir AA, Mosbah A, Abol-Enein H, Barakat N, Abou-Bieh E, et al. Recoverability of renal function after relief of chronic partial unilateral ureteral obstruction: study of the effect of angiotensin receptor blocker (losartan). Urology. 2010;75(4):848-52. doi: 10.1016/j.urology.2009.07.1217.
30. Manucha W, Carrizo L, Ruete C, Molina H, Vallés P. Angiotensin II type I antagonist on oxidative stress and heat shock protein 70 (HSP 70) expression in obstructive nephropathy. Cell Mol Biol (Noisy-le-grand). 2005;51(6):547-55.
31. Kopp UC. Neural control of renal function. Compr Physiol. 2011;1(2):731-67. doi: 10.1002/cphy.c100043.
32. Misseri R, Rink RC, Meldrum DR, Meldrum KK. Inflammatory mediators and growth factors in obstructive renal injury. J Surg Res. 2004;119(2):149-59. doi: 10.1016/j.jss.2004.02.016.
33. Hammad FT, Wheatley AM, Davis G. Long-term renal effects of unilateral ureteral obstruction and the role of endothelin. Kidney Int. 2000;58(1):242-50. doi: 10.1046/j.1523-1755.2000.00159.
34. Durvasula RV, Petermann AT, Hiromura K, Blonski M, Pippin J, Mundel P, et al. Activation of a local tissue angiotensin system in podocytes by mechanical strain. Kidney Int. 2004;65(1):30-9. doi: 10.1111/j.1523-1755.2004.00362.
35. Laplante M-A, Wu R, Moreau P, de Champlain J. Endothelin mediates superoxide production in angiotensin II-induced hypertension in rats. Free Radic Biol Med. 2005;38(5):589-96.doi:10.1016/j.freeradbiomed.2004.11.026.
36. Suzuki Y, Lopez-Franco O, Gomez-Garre D, Tejera N, Gomez-Guerrero C, Sugaya T, et al. Renal tubulointerstitial damage caused by persistent proteinuria is attenuated in AT1-deficient mice: role of endothelin-1. Am J Pathol. 2001;159(5):1895-904. doi: 10.1016/S0002-9440(10)63036-2.
37. Wenzel R, Rüthemann J, Bruck H, Schäfers R, Michel

M, Philipp T. Endothelin-A receptor antagonist inhibits angiotensin II and noradrenaline in man. Br J Clin Pharmacol. 2001; 52(2): 151-7. doi: 10.1046/j.0306-5251.2001.01422.

38. Fabiani ME, Sourial M, Thomas W, Johnston CI, Frauman AG. Angiotensin II enhances noradrenaline release from sympathetic nerves of the rat prostate via a novel angiotensin receptor: implications for the pathophysiology of benign prostatic hyperplasia. J Endocrinol. 2001;171(1):97-108.
39. Ito K, Chen J, El Chaar M, Stern JM, Seshan SV, Khodadadian JJ, et al. Renal damage progresses despite improvement of renal function after relief of unilateral ureteral obstruction in adult rats. Am J Physiol Renal Physiol. 2004;287(6):F1283-93. doi: 10.1152/ajprenal.00441.2003.
40. Yoo K, Norwood V, El-Dahr S, Yosipiv I, Chevalier R. Regulation of angiotensin II AT1 and AT2 receptors in neonatal ureteral obstruction. Am J Physiol Regul Integr Comp Physiol. 1997; 273(2):R503-R9.
41. Tanyong J, Eiam-Ongb S, Phansuwan P, Eiam-Ong S. Role of angiotensin II on protein expression of renal nitric oxide synthase in unilateral ureteral obstructive rat. Asian Biomed. 2011;5(3):2-4. doi:10.5372/1905-7415.0503.044.
42. Batenburg WW, Garrelds IM, Bernasconi CC, Juillerat-Jeanneret L, van Kats JP, Saxena PR, et al. Angiotensin II type 2 receptor–mediated vasodilation in human coronary microarteries. Circulation. 2004;109(19):2296-301. doi: 10.1161/01.CIR.0000128696.12245.57.
43. de Castro CH, dos Santos RAS, Ferreira AJ, Bader M, Alenina N, de Almeida AP. Evidence for a functional interaction of the angiotensin-(1–7) receptor Mas with AT1 and AT2 receptors in the mouse heart. Hypertension. 2005;46(4):937-42. doi: 10.1161/01.HYP.0000175813.04375.
44. Kostenis E, Milligan G, Christopoulos A, Sanchez-Ferrer CF, Heringer-Walther S, Sexton PM, et al. G-protein–coupled receptor Mas is a physiological antagonist of the angiotensin II type 1 receptor. Circulation. 2005;111(14):1806-13. doi: 10.1161/01.CIR.0000160867.23556.
45. Maleki M, Nematbakhsh M. Gender difference in renal blood flow response to angiotensin II administration after ischemia/reperfusion in rats: the role of AT2 receptor. Adv Pharmacol Sci. 2016;2016:7294942. doi: 10.1155/2016/7294942.