www.nephropathol.com DOI: 10.15171/jnp.2019.01 J Nephropathol. 2019;8(1):e01

Journal of Nephropathology

Renoprotective impact of angiotensin 1-7: Is it certain?

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ARTICLE INFO

Article type:
Short-Review

Article history:
Received: 7 February 2018
Accepted: 29 June 2018
Published online: 6 August 2018

Keywords:
Renin angiotensin system
Angiotensin II
Angiotensin1-7
Vascular endothelium
Kidney injury
Bradykinin receptors

ABSTRACT

The two important arms of renin angiotensin system (RAS) are angiotensin II (Ang II) and angiotensin1-7 (Ang1-7). Both of these peptides are present in the kidney, while the renal hemodynamic responses to these peptides act differently in kidney circulation.
For this short-review, we used a variety of sources including PubMed, Google Scholar, and Scopus.
Although in normal physiological condition, Ang1-7 has been known as an inactive agent in the renal system, however in past years many experimental and clinical reports indicated the protective role of Ang1-7 in renal hemodynamics and functions under different circumstances. In the current article, the possible renoprotective role of Ang1-7 was briefly reviewed.

Short-Review

Implication for health policy/practice/research/medical education:
The protective role of angiotensin 1-7 in renal system mostly related to the improvement of endothelial function or struggle with serious hazard and damage induced by angiotensin II in the kidney.

Please cite this paper as: Nematbakhsh M. Renoprotective impact of angiotensin 1-7: Is it certain? J Nephropathol. 2019;8(1):e01. DOI: 10.15171/jnp.2019.01.

1. Introduction

Renin angiotensin system (RAS) plays an important role in kidney function; especially in controlling renal hemodynamics. Angiotensin 1-7 (Ang1-7) is known as an effective bioactive heptapeptide in RAS, and it has a concentration of 20 pg/mL in blood (1) with 10 seconds of half-life (2, 3). Ang1-7 is presented in kidney, heart, testis, and vascular endothelium (4). It inserts its action via Mas receptor (MasR) which was found in 1986 (5-7). However, Ang1-7's metabolism in the kidney performs through different pathways (8,9). There is an interaction between two important arms of RAS; Ang1-7 and AngII in the kidney (10), while Ang1-7 also could bind to AngII receptors (AngII type 1 and 2 receptors; AT1R and AT2R) (11). The angiotensin converting enzyme (ACE) is antagonized by Ang1-7 (12), and ACE inhibitors increase the plasma and urine levels of Ang1-7 (13). It is reported that the level of Ang1-7 in end-stage renal disease is higher than normal level which is increased by ACE inhibitors (14). Ang1-7 and AngII perform different actions in vascular system, and actually Ang1-7 function is against classical performance of AngII by antagonizing AngII-AT1R axis. In terms of Ang1-7 effects on the AngII, Ang1-7 could reduce renal AT1R (15). Usually, lowering blood pressure, inhibition of cell growth, reduction of inflammation, increasing urine flow, sodium excretion and improvement of endothelial function are some of the actions that may be induced by Ang1-7. Despite the extensive studies that have been done in recent years on the protective effects of Ang1-7 on renal system and suggested mechanisms, the definitive effect of Ang1-7 in the kidney may not be precisely explained.

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2. Materials and Methods

For this short-review, we used a variety of sources including PubMed, Google Scholar and Scopus. The search was conducted by using combinations of the following key words and or their equivalents; renin angiotensin system, angiotensin II, angiotensin1-7, kidney circulation, and renal function.

3. Local renal Ang1-7

ACE2 is present in the kidney abundantly and about 42 percent is similar to ACE. Ang1-7 and its specific receptor MasR are found in different parts of the kidney while intra-renal formation also is suggested (5, 13). One mechanism suggested that the expression of Ang1-7 may augment via reduction of enzyme dipeptidyl peptidase in HK-2 renal epithelial cells (16). There is an evidence that renal Ang1-7 may be generated within mitochondria, and it involves in mitochondrial function (17). The component of biological membranes includes phosphatidylcholine which its biosynthesis in renal cortex is increased by Ang1-7 (18). The renal formation of Ang1-7 in pathological conditions or in knockout animal models provides some additional data related to this peptide in the renal system. The kidney's Ang1-7 alteration may not depend on systemic circulation changes as reported that the local renal level of Ang1-7 reduced after renal ischemia/reperfusion while no change in the plasma level and renal expression of ACE2 were detected (19). In AT2R knockout mice, the renal level of Ang1-7 decreased which revealed the direct or indirect effect of AT2R on the kidney's Ang1-7 level (20). However, in such model the kidney injury induced by high fat diet promotes by increasing the cortical expression of AT1R (20). The in-vitro study indicated that Ang1-7 may prevent aldosterone induced α-smooth muscle actin expression and decrease the secretion of collagen type 1 in renal fibroblasts (21).

Ang1-7 is catalyzed through AngII/ACE2 pathway. The existence of renal Ang1-7 in ACE2 knockout mice indicated the involvement of other enzymes in Ang1-7 formation in the kidney (22). The Ang1-7 peptidase within proximal tubule may regulate Ang1-7 tone (23). Undoubtedly, the local formation of Ang1-7 in the kidney is definite, but the exact mechanisms may vary depending on the circumstances, and its dimensions are not completely well understood yet.

4. Renal vascular response to Ang1-7

Ang1-7 has been known as an inactive agent in the renal vascular system in normal physiological condition, but it antagonizes the vascular effects of AngII (24). However, in past years many attentions were made to specify the exact effect of Ang1-7 in renal vascular bed. The Ang1-7 induced vasorelaxation action in isolated renal artery was endothelium related which could be reduced by AngII (AT1R, AT2R), and bradykinin receptors antagonists (25). The Ang1-7 induced vasodilation was reduced when renin secretion system activated in renal artery stenosis (26). Others observations indicated that the vasodilatory effect of Ang1-7 was depended on sodium of diet and AngII level (27, 28). In addition, the chronic treatment of Ang1-7 improves the renal endothelial function in atherosclerosis (29). The renal circulation also is influenced by Ang1-7 via increase of renal blood flow (RBF) and decrease of renal vascular resistance (RVR). The reduced RBF induced by hemorrhagic shock was restored by Ang1-7 infusion, and this peptide action for increasing RBF was similar to hyperosmotic fluid infusion (30). Handa et al reported that the increased RBF and the decreased RVR induced by Ang1-7 are mediated with p38 mitogen-activated protein kinase in apoE(-/-) mice (31). On the contrary, Ang1-7 administration with the dose greater than 1 nmole/kg also was shown to decrease RBF (32). The renal vascular response to Ang1-7 also was gender and sex hormone related. Although the MasR has been known as specified receptor for Ang1-7 however, by MasR antagonist (A779) infusion, the RBF response to Ang1-7 may attenuate in female, and such observation was not seen in male (33). Moreover, by inhibition of AngII receptors (AT1R and AT2R) and Ang1-7 receptor (MasR), the RBF response to Ang1-7 infusion increased in male (not in female) (34). These results bring a conclusion that RBF response to Ang1-7 may exert via different pathways from the MasR line (33, 34). We also reported before, when MasR was blocked, the RBF response to Ang1-7 in female ovariectomized estradiol treated rats was attenuated compared to non-estradiol treated rats (35) by an unknown mechanism. Other report indicated that RBF increased by Ang1-7 may be not observed when MasR, prostaglandin and nitric oxide are limited (36). In diabetic hypertensive model, Ang1-7 decreased vascular response to endotheline-1, norepinephrine and AngII (37) while other study indicated that Ang1-7 could not attenuate the vascular effect of AngII administration (38). The renal vasculature response to Ang1-7 was different in hypertensive and diabetic models. The induced renal pressure responses to AngII in both models was reduced by Ang1-7, however the ability to reduce these responses in the renal of hypertensive model was greater than diabetic model , and the effect of Ang1-7 was not abolished by AT2R antagonists, but mediated by prostaglandins and nitric

oxide (NO) systems (39). Collectively, it seems that renal hemodynamics response to Ang1-7 in physiological and pathophysiological circumstances may be varying by the kidney conditions. Different results from the effect of Ang1-7 on the renal blood flow (9, 31, 38) and the obtained gender related response of RBF to Ang1-7 (33, 34) may open a new window to think about other pathways possibly excluding MasR in which Ang1-7 could alter renal hemodynamics responses.

5. Renal function response to Ang1-7

As mentioned, in normal physiological condition Ang1-7 may not play an important role in kidney function regulation. However, this peptide's actions on renal function alter considerably based on kidney condition as alteration of RAS function change the Ang1-7's actions (40). Ang1-7 administration performs diuresis and natriuresis that may inhibit by MasR or AT1R antagonists (41). This peptide may not change glomerular filtration rate (GFR), but it reduces renal plasma flow and renal sodium excretion (38). Against this finding, Ang1-7 induced an increasing of GFR (42). The urine flow response to Ang1-7 increased in male and female rats (43). However, the increased urine flow and fractional sodium excretion induced by Ang1-7 infusion were decreased in low sodium diets compared to normal diet (41). The formation of stress oxidative, fibrosis and inflammation induced by the chronic hypoxia renal injury was reported to reduce by Ang1-7 (44). In other renal injury models such as high fat diet in AT2R knockout rats, the renal level of Ang1-7 decreases while increasing AngII level (20). In addition, an interaction between Ang1-7 and AngII was observed in renal mesangial cells (45). However, Esteban et al concluded that the pro-inflammatory effect of Ang1-7 mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and MasR but not through AngII receptors (46). Ang1-7 counter-regulates the deleterious effects of AngII. It could be improved the kidney fibrosis and inflammation by different pathways such as extracellular-signal regulated kinase (ERK) (47). Renal function improvement and reduction of oxidative stress and glomeruli sclerosis were found by administration of Ang1-7 in streptozotocin induced diabetic nephropathy rats (48). On the other hand, Shao et al demonstrated that Ang1-7 infusion decreased the AT2R and MasR expression and disturbed renal function in streptozotocin diabetic rats (49). There is an association between diabetic nephropathy and renal Ang1-7 level (50) while Ang1-7 administration reduced glomerular damage and oxidative stress to promote kidney function in type 2 diabetic (db/db) mice (51). Shi et al used diabetic Akita mice model and the animals were treated with Ang1-7 with and without MasR antagonist for six weeks, and the result indicated that Ang1-7's action exerted via MasR protected the kidney function by reduction of some markers such as urinary albumin/creatinine ratio and tubular apoptosis, and kidney oxidative stress reduction (52). On the contrary, Gonzales et al reported that Ang1-7 induces oxidative stress (thiobarbituric acid reactive substance) and decrease glutathione levels in the kidney (53).

The function of Ang1-7 also has interaction with corticosteroid as Bi et al, demonstrated that Ang1-7 decreased sodium excretion in betamethasone treated sheep, and AT1R antagonist candesartan limited this response (54). The development of glomerular injury is accompanied with ACE2 inhibition (55) while the renal production of atrial natriuretic peptide (ANP) is depended on ACE2/Ang1-7 pathway (56). The reduction of proteinuria and kidney tissue damage in stroke-prone spontaneously hypertensive rats were detected by Ang1-7 administration via alteration in interleukin-6, tumor necrosis factor and NF-kB levels (57). In the model of hypertensive (renal wrap model) ovariectomized rats, ACE2 activity was reduced, and Ang1-7 protected the kidney against ovariectomy (58) while in diabetic hypertensive model, Ang1-7 decreased the degree of proteinuria and renal NADPH oxidase activity (37). In 2K1C hypertensive model, Ang1-7 did not alter kidney function, but Ang1-7 deficiency may accelerate hypertension (59). Ferreira et al utilized the transgenic rats with a higher plasma level of Ang1-7, and they found no morphology and V2 receptor changes, however, a decrease of urine flow and free water clearance and an increase in urine osmolality were detected (60). This funding suggests the effective role of Ang1-7 in water balance independent of anti-diuretic hormone. Kim et al reported that in unilateral ureteral obstruction animals subjected to treatment with Ang1-7, less renal apoptosis and fibrosis and more ACE2 expression was detected (61). The protective role of Ang1-7 administration on renal function in an animal model of 5/6 nephrectomy was evident by the lower serum creatinine, proteinuria and glomerulosclerosis (62) while another study which utilizes such animal model suggested the protective role of endogenous ACE2 in chronic kidney disease (63). The ACE inhibitor such as captopril increases the plasma level of Ang1-7 (64). Finally, the relation between renal Ang1-7 and renal sympathetic nerve activity also is important. Recently Silva et al by microinjection of MasR antagonist into paraventricular hypothalamic

nucleus (PVN) suggested that Ang1-7 in PVN involves the renal nerve activity (65).

6. Conclusions

The protective role of Ang1-7 in renal system mostly related to the improvement of endothelial function or struggle with serious hazard and damage induced by AngII in the kidney (66). However, the paradoxical protective role of Ang1-7 was mentioned before which is related to various parameters (67). Still, the certain protective conclusion for Ang1-7 in the renal system is a bit crude, but in general hopes for future are visible.

Author's contribution

MN is the single author of the paper.

Conflicts of interest

The author declares no conflict of interest.

Ethical considerations

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

Funding/Support

This research was supported by Isfahan University of Medical Sciences.

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