Renin angiotensin system and different mediators induce renal fibrosis

Amin Hasanvand[1], Shadan Saberi[2*]

Abstract
Renal fibrosis (RF) is the final step in chronic kidney disease (CKD) that is represented by abundant extracellular matrix (ECM) components, tubular atrophy and inflammatory cell infiltration. Renal failure results from a series of factors as follows; the activation of cytokines due to the entrance of bioactive molecules of plasma to the tubulointerstitial space, the activation of signal molecules such as transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), the activation of renin angiotensin system (RAS) especially angiotensin II (Ang II), endothelin-1, other pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), and finally endothelial to mesenchymal transition. Among all factors, this review focuses on RAS by considering the role of component of two axes of this system and mediators involved in RF. Ang II participates in many chronic diseases such as hypertension and chronic heart disease. Moreover, ACE/Ang II/ATR axis exhibits a fibrogenic effect while angiotensin (1-7) reveals both anti-fibrotic and fibrotic effects. However, most researchers believe in the renoprotective effect of ACE2/Ang 1-7/MasR axis. The ratios of activities of these two axes determine the progression or inhibition of RF. Several signaling pathways and cytokines play role in RF but TGF-β is the most important mediator. The existence of a feedback relationship between TGF-β and RAS is considered in this study.
Keywords: Renal fibrosis, Renin angiotensin system, Angiotensin II, Angiotensin (1-7), pro-inflammatory cytokines
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Introduction

Chronic kidney disease (CKD) is the most important problem in nephropathology that starts by diseases such as diabetic nephropathy, obstructive nephropathy, cystic nephropathies, glomerulonephritis or interstitial nephritis and ends in renal fibrosis (RF) for which the patient needs to undergo dialysis and transplantation (1-3).

Materials and Methods

For this review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; renal fibrosis, renin angiotensin system, angiotensin II (Ang II), angiotensin (1-7) (Ang 1-7), pro-inflammatory cytokines, chronic kidney disease and end-stage renal disease

Papers published in English as full-text articles and or as abstracts were included in this study.

End-stage renal disease

End-stage renal disease (ESRD) is the final pathologic state of CKD that is represented by extra-accumulation and

deposition of extracellular matrix (ECM) components, tubular atrophy and inflammatory cell infiltration (4). The entrance of bioactive molecules of plasma into the tubules from injured glomerular barrier leads to the generation and activation of different cytokines and infiltration of monocytes into the tubulointerstitial space (4,5). Infiltrated monocytes could produce inflammatory and fibrogenic cytokines and reactive oxygen species (ROS) (4). This phenomenon ultimately results in ECM accumulation (6). Another mechanism involved in the production of extra ECM is the activation of signal molecules such as transforming growth factor beta (TGF-β) which is the most important molecule mediates RF in CKD (7,8). Origin of TGF-β might be renal cells, infiltrated leukocytes or plasma (7). TGF-β1 stimulates (Smad2 and Smad3) or inhibits (Smad7) fibrosis through Smad family (9). TGF-β plays an important role in several steps of fibrosis development including stimulation of myofibroblastic activation, transition of mesangial cells and interstitial fibroblasts, and finally production of fibrogenic cells in matrix from tubular epithelial cells (8,9). Overexpression of TGF-β caused glomerular and interstitial fibrosis in transgenic mice (10). Renin angiotensin system (RAS)

[1]Department of Pharmacology and toxicology, Faculty of pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran. [2]Department of Physiology and Pharmacology, Kerman University of Medical Sciences, Kerman, Iran.
***Corresponding Author:** Shadan Saberi, Email; shdnsbr@yahoo.com

activation participates in inflammation and fibrosis (11-13). Angiotensin II (AngII) is the main effector in RAS that is involved in this process (11). Ang II (AT1R) influences growth factors such as TGF-β and results in ECM accumulation via binding to angiotensin II type 1 receptor (11). Increment of other growth factors such as connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF) in tubulointerstitial area of fibrotic kidney was observed and proposed to have a potential role in RF (14-16). Endothelial-mesenchymal transition (EMT) is known as a new mechanism involved in the development of interstitial fibrosis in different organs including kidney (17), blood vessels (18) and lung (19). EMT is a four-step process in which endothelial cells achieve mesenchymal (myofibroblasts) properties like expression of α smooth muscle actin (α-SMA) and actin (20). Myofibroblasts are very important in producing and secreting of ECM in the progression of RF (21). The rise of local growth factors, especially TGF-β, could simplify EMT (22,23). Moreover, endothelin-1 (ET-1) is a potent vasoconstrictor that is plentiful in renal endothelial cells, and induces pro-fibrotic as well as pro-inflammatory effects (24). Due to vasoconstriction and hypoxic condition resulting from ET-1, mesangial cells were proliferated and ECM was produced (25,26). Other pro-inflammatory cytokines that might interfere in RF are tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) (27,28). As mentioned above, various factors participate in the pathogenesis of RF due to the significant role of RAS in pathophysiology of kidney. However, this review focuses mainly on RAS and fibrogenic activity of Ang II and AT1R. However, there is the question on roles of other receptors or Ang 1-7 in RF. This article aimed to notice the importance of RAS peptides, receptors and enzymes separately in two distinct axes. It also indicates the mechanisms mediated by this system.

ACE/Angiotensin II/ATR

The most significant effector of the RAS is Ang II the effects of which are mediated by two main receptors of AT1 and AT2 (29). Ang II takes part in chronic diseases, like hypertension and cardiac hypertrophy

(11). Moreover, Ang II plays an important role in renal diseases by modulating inflammation and fibrosis (30,31). Different mediators and signaling pathways are involved in the fibrogenic action of Ang II. This peptide induces fibrogenesis through the synthesis of chemotactic factors, such as monocyte chemoattractant protein-1 (MCP-1) (32). Ang II increases cell growth in kidney via ECM proteins enhancement and activation of mesenchymal and tubular cells and interstitial fibroblasts (32). It seems that growth factors are involved in this effect. Angiotensin II type 1 receptor (AT1R) mediates regulation of TGF-β and CTGF expression (11,31,33). Moreover, AT1R activates Rho/Rho kinase signaling pathway that participates in the progression of RF (34). Rho is a small protein that starts up different cellular functions such as the production of cytokines (35). Rho kinase inhibitors such as Y-27632 or fasudil decreased tubulointerstitial fibrosis in kidney by diminishing CTGF up-regulation and inflammatory cells proliferation (36,37). Gene expression of several pro-inflammatory cytokines, chemokines and adhesion molecules are affected by Ang II via AT1R including interleukin-6 (IL-6), MCP-1, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) (30). Different signaling pathways are involved in the regulation of mediators such as Rho proteins, nuclear factor-KB (NF-KB), mitogen-activated protein kinase (MAPK) and redox pathways (30). NF-KB activated by Ang II decreased by AT1R and AT2R antagonist or ACE inhibitors (32,38). Telmisartan, an AT1R blocker, reversed up-regulation of TGF-β1, p38MAPK, collagen III in diabetic mice, which leads to reduce fibrosis injury in kidney (39). Diabetic nephropathy is a pathogenic condition that is accompanied by RAS activation, Ang II elevation, NF-KB activation and up-regulation of pro-inflammatory genes (40). Another pathologic condition resulting in RF is unilateral ureteral obstruction. TGF-β plays a very significant role in fibroblast differentiation of unilateral ureteral obstruction animal model (41-43). Takeda et al reported that co-administration of fasudil and an ACE inhibitor have more efficiency than monotherapy in suppressing fibroblast differentiation which leads to deposition of ECM and fibrosis (44). Macrophage/ monocyte infiltration which is regarded as the major action in the progression of RF in unilateral ureteral obstruction model could stimulate oxidative stress, TGF-β elevation and cytokine production (42,45). Combination therapy decreased TGF-β by reducing macrophage/monocyte infiltration (44). It seems that when Rho kinase inhibition was added to the ACE inhibition, that is the most common treatment of renal disease, greater benefits were achieved compared to performing merely the therapy (44). The role of AT2R is not well understood till now, but few studies consider a protective role against AT1R fibrotic function for this receptor (46,47). AT2R knockout (AT2RKO) mice have revealed properties of diabetic nephropathy in type 1 diabetic model (48). Increment of RAS components including AT1R and ACE and decrement of angiotensin

converting enzyme 2 (ACE2) was seen in AT2RKO mice. Furthermore, oxidative stress and generation of ROS in kidney of these mice increased (48). These observations could explain diabetic nephropathy in AT2RKO mice (48). The importance of AT2R stimulation was studied in the two-kidney, one-clip (2K1C) rat model of hypertension (49). Pro-inflammatory agents such as TNFα, TGF-β1, and IL-6 expression decreased in response to treatment with C21, an AT2R agonist (49). Inflammatory cell infiltration and totally renal injury to the tubules and glomerulosclerosis were reduced by C21 administration (49). The antagonist of AT2R revealed a renoprotective effect when applied in early phase in a partial nephrectomized model (50). Other researchers began their intervention in the presence of glomerulosclerosis in order to stimulate CKD and study the effect of AT2R in delayed phase of kidney disease (51). They observed that not only AT2R blockade does not have any advantages but also it prevents AT1R blockers (ARB) advantages on sclerosis and proteinuria in combination therapy (51). AT2R antagonists block AT2R and simultaneously up-regulate a subtype of AT1R called AT1B. Therefore, the final effect might be determined by AT1R to AT2R ratio (51). Since AT2R function in RF is not completely clear, more studies are required to elucidate controversies.

ACE2/Angiotensin 1-7/MasR

For several years, information about RAS was restricted to classic axis and ACE/Ang II/ ATRs until the discovery of Ang 1-7 as an active heptapeptide in the late 1980s (52,53). ACE2 was discovered as the main enzyme to degrade Ang I and mostly Ang II into Ang 1-7 (54,55). The G-protein coupled receptor called Mas is the mediator of Ang 1-7 (56). Thus ACE2/Ang 1-7/MasR is a new axis of RAS with beneficial effects such as vasodilation, anti-proliferation, anti-fibrosis, anti-thrombosis and anti-arrhytmia (57-61). Moreover, this protective axis of RAS attenuate inflammation and deposition of collagen (62). Ang 1-7 prohibited cardiac fibrosis in response to Ang II in Sprague-Dawley rats (60). The heptapeptide reduced fibrosis in heart in 2K1C hypertensive rats (63). Furthermore, the up-regulation of AT2R and MasR was observed in this animals (63). ECM proteins might be involved in anti-proliferative and anti-fibrotic effect of MasR since the MasR-deficient mice revealed greater amounts of collagen type I and III but fewer collagen IV in heart (64). AVE0991, A MasR agonist or Ang 1-7 administration reduced migration and adhesion of leukocytes to the endothelium of microvasculars at swollen joints in arthritis model (65) Moreover, Ang 1-7 reduced inflammatory cell infiltration and pulmonary fibrosis in murine model of asthma (66). In diabetic nephropathy, ROS generation is related to RAS activation (67,68) and diabetic condition leads to hyperactivity of pro-inflammatory and pro-fibrotic cytokines and growth factors which develop fibrosis (69). This study indicated that RF decreased after treatment by Ang 1-7 in db/

db mice (69). STAT3 phosphorylation was involved in the progression of fibrosis and increased in kidney of db/db mice but Ang 1-7 reversed this effect (69). Other studies revealed that MAPK phosphorylation, TGF-β1 expression, fibronectin and collagen IV induced by Ang II, decreased via Ang 1-7 (70). It could be concluded that Ang 1-7 counteracted the inflammatory and fibrogenic functions of Ang II through affecting mediators and signaling pathways which were activated by Ang II. The chronic administration of ACE inhibitors and ARBs increased Ang 1-7 plasma level and changed balance between Ang II and Ang 1-7 concentrations that could be the mechanism of renoprotective action of these drugs (71-73). ACE2 is the homolog of ACE which is responsible to stop the effect of Ang II by breaking this octapeptide to Ang 1-7 (54,55). Several studies consider a protective role for ACE2 (74-76). For instance, in bleomycin induced pulmonary fibrosis expression and function of ACE2 were attenuated in rats and mice (74). Moreover, ACE2 inhibition resulted in pulmonary Ang II level increment and severe bleomycin induced pulmonary fibrosis (74). ACE2 deficiency caused overexpression of inflammatory cytokines and chemokines induced by Ang II in aorta (75). On the other hand, the overexpression of ACE2 prevented the rise of MCP-1 induced by Ang II through increasing 1-7 levels of Ang (77). In 5/6 nephrectomy, the mice inhibition of ACE2 resulted in an AT1R mediated proteinuria (76). Moreover, chronic ACE2 inhibition induced proteinuria in normal and diabetic mice (78). High amounts of TNF-α, IL-6 and MCP-1 in addition to the development of inflammation, tubulointerstitial fibrosis and increase of Ang II in comparison to Ang 1-7 result from ACE2 deficiency in unilateral ureteral obstruction model (79). Physio-pharmacological researches represent that ACE2/Ang 1-7/MasR axis activation is involved in the beneficial effect of ARBs to prevent inflammation (80,81). Effect of ARBs consists of overexpression of ACE2, Ang 1-7 and MasR in addition to up-regulation of anti-inflammatory cytokine, IL-10 and down-regulation of pro-inflammatory cytokines like IL-1β, IL-6, TNF-α and interferon γ (IFN- γ) (80,81). As stated above, TGF-β is the most important cytokine in inflammation and fibrosis (82). There is evidence in the literature to show that ACE2/Ang 1-7/MasR axis regulates TGF-β expression (83,84). Administration of Ang 1-7 fusion gene, that is conducted 2 weeks before receiving bleomycin, prevented the rise of TGF-β mRNA level, generation of other pro-inflammatory cytokines and pathophysiological alteration that led to pulmonary fibrosis (83). Ang 1-7 slowed down the rise of TGF-β and collagen I mRNA level induced by cardiac infarction (84). On the other hand, TGF-β1 could attenuate ACE2, MasR and conversion of Ang II to Ang 1-7 via a negative feedback (85). It seems that a feedback relationship exists between ACE2 and TGF-β (85). A few studies consider a stimulatory effect for ACE2/Ang 1-7/MasR axis in renal injury (86). For example, MasR deficiency reduced renal injury in unilateral ureteral

obstruction and ischemia/reperfusion. Moreover, Ang 1-7 administration in normal mice induced inflammation (87), while 5 days administration of Ang 1-7 ameliorated glomerulosclerosis (88). This controversy could be explained by different pathological conditions that were studied, RAS activation, route or dose of administration and variation in signaling pathways (86). Furthermore, Ang 1-7 signaling pathway is cell specific, for instance, in proximal tubule of nephron exhibits a growth inhibitory action that is against the effect of Ang II (89), whereas it displays a stimulatory effect on mesangial cells which is mediated by MAPK phosphorylation (90). These effects of Ang 1-7 are MasR dependent but not AT1R or AT2R dependent (90). In spite of all the controversies observed in Ang 1-7 administration, most experiments suggest a renoprotective effect.

Conclusion

ESRD is the final clinical problem in CKD which leads to renal failure and dialysis and transplantation. Several factors participate in RF but this article focused on RAS among all of them. Ang II is a fibrogenic factor that mediates ECM proteins production, pro-inflammatory cytokines infiltration and expression through different growth factors (TGF-β, CTGF) or signaling pathways such as NF-Kβ, MAPK phosphorylation, Rho kinase and redox pathways via AT1R. The effect of AT2R is mainly against AT1R and time-dependent while it is not completely understood. Ang 1-7 counteract Ang II fibrogenic effects thorough mediating ECM proteins, inflammatory cell infiltration in reverse side and also by affecting the same signaling pathways. In short, both RAS axes play roles in RF in the kidneys. Moreover, the major determinant parameter is the ratio of enzyme activity of this system (ACE/ACE2) and the ratio of their product (Ang II/Ang 1-7).

Authors' contribution
SS and AH searched the literature and wrote the manuscript equally.

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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