Physiology and Pharmacology

Physiol Pharmacol 21 (2017) 266-278 **www.phypha.ir/ppj**

Review Article

Renin-angiotensin system and unilateral ureteral obstruction

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Abstract

Unilateral ureteral obstruction (UUO) is a clinical scenario that leads to obstructive nephropathy. UUO alters the expression of many mediators in the ipsilateral kidney. Renin-angiotensin system (RAS) is involved in UUO. Angiotensin II (Ang II) and angiotensin 1-7 (Ang 1-7) as the main arms of RAS influence kidney function which may alter by UUO. Ang II via Ang II receptor subtypes I (AT_1R) reduces renal blood flow and glomerular filtration rate and induces oxidative stress, apoptosis as well as inflammation in renal tissue and contributes to renal fibrosis in UUO model. Also, Ang 1-7 receptor (MasR) and Ang II receptor subtype II (AT_2R) may have a protective effect against UUO-induced renal injury. In addition, there is crosstalk among RAS with the main vasodilator factors (prostaglandins E2 and I_2, bradykinin, atrial natriuretic factor, nitric oxide and adenosine) and the main vasoconstrictor factors (endothelin and vasopressin) in the ipsilateral kidney with UUO. In this review, the roles of the RAS on renal function and its interactions with the other factors in the kidney with UUO were discussed.

Keywords:
Renin-angiotensin system;
Unilateral ureteral obstruction;
Kidney injury;
Angiotensin II;
Angiotensin 1-7

Received: 1 Aug 2017
Accepted: 29 Oct 2017

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Introduction

Unilateral ureteral obstruction (UUO) is often recognized as a clinical disorder due to trauma, obstructing stone, tumors and endometriosis (Heyns, 2012). The study of kidney disease has shown that the experimental model of UUO and human obstructive nephropathy have the same effect and symptoms on ipsilateral kidney suffering from UUO (Nogueira et al., 2017). UUO impairs the kidney function and induces kidney injury. Clinically, UUO through blocking the normal urine flow disrupts the kidney structure and leads to renal dysfunction, hydronephrosis, and kidney enlargement (López-Novoa et al., 2010). UUO as an animal model, widely used for examining the non-immunological mechanisms of tubulointerstitial fibrosis (Grande et al., 2010). After UUO, intratubular pressure and tubule walls extension rise (Klahr and Morrissey, 2002). These conditions lead to renal fibrosis indicators increasing, epithelial tubular cell damage (Grande et al., 2010), matrix deposition, fibrosis development and tubular atrophy (Nogueira et al., 2017; Tan et al., 2007). Renin-angiotensin system (RAS) plays an important role for pharmacological intervention in the kidney with UUO (Frokiaer, 2005). As specified, two main arms of RAS are angiotensin II (Ang II) and angiotensin 1-7 (Ang 1-7) which are present in the renal system (Saberi et al., 2016). Ang II exerts its biological effects via Ang II receptor subtypes I (AT_1R) (Zhang and Sun, 2006) and

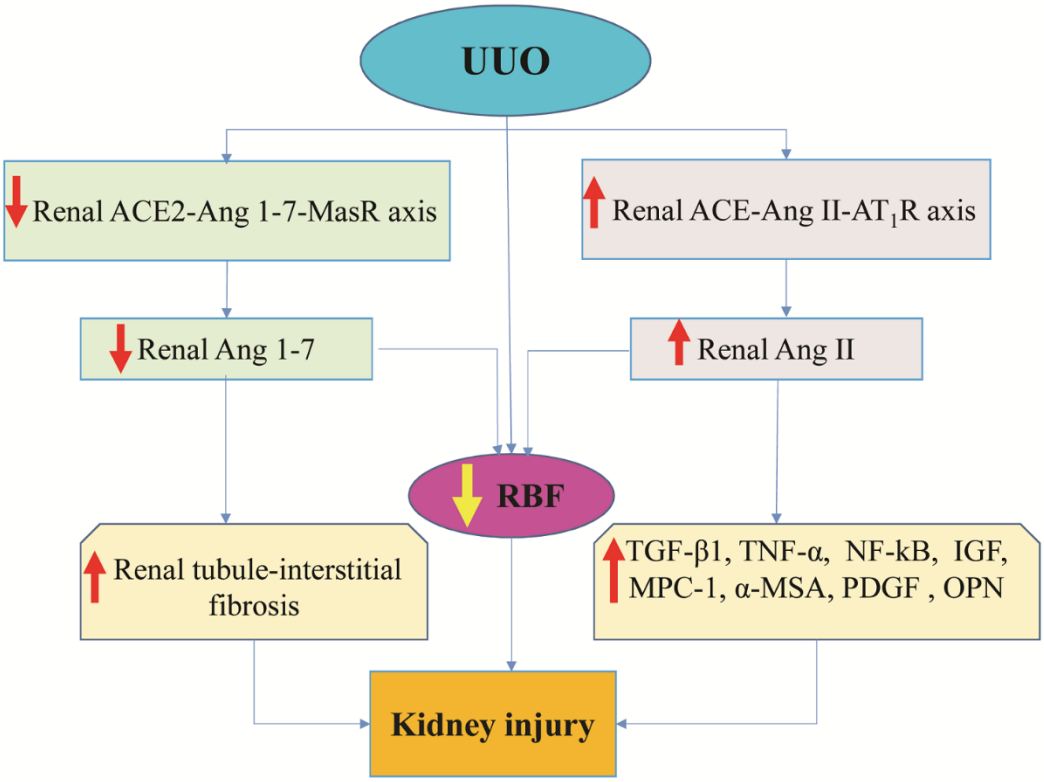

Fig.1. Schematic representation for the role of UUO and RAS system in renal fibrosis and kidney injury. UUO: Unilateral ureteral obstruction, ACE: Angiotensin-converting enzyme, MasR: Angiotensin 1-7 receptor, ACE2: Angiotensin-converting enzyme 2, Ang 1-7: Angiotensin 1-7, Ang II: Angiotensin II, RBF: Renal blood flow, TGF-β1: Transforming growth factor -β1, TNF-α: Tumor necrosis factor-α, NF-kB: Nuclear factor kappa-B, IGF: Insulin-like growth factor, MCP-1: Monocyte chemotactic protein-1, α-SMA: Alpha-smooth muscle actin, PDGF: Platelet-derived growth factor, OPN: Osteopontin. The up-arrow and down-arrow represent increase or decrease.

subtypes II (AT_2R) in renal tissue (Hilliard et al., 2011), and Ang 1-7 acts via Mas receptor (MasR) (Mansoori et al., 2014). Observations show that there is crosstalk among AT_1R, AT_2R and MasR in the kidneys and also they form heterodimers to talk together (Safari et al., 2012; Su, 2014). In obstructive nephropathy, Ang II via AT_1R induces renal injury and via AT_2R has contrast effects (Benndorf et al., 2009). Ang II intervenes in function and hemodynamic parameters in the ipsilateral kidney with UUO (Topcu et al., 2007). Contradictory reports have seen about the role of AT_2R and MasR in inducing or inhibiting the fibrosis and apoptosis in the kidney with UUO (Kellner et al., 2006). Moreover studies have shown that there is crosstalk between RAS with endothelin (Kohan et al., 2011), vasopressin (Wong and Tsui, 2003), bradykinin (Huart et al., 2015), nitric oxide (NO) (Heitsch et al., 2001), adenosine (Lai et al., 2006b), atrial natriuretic peptide (ANP) (Bae et al., 2007), prostaglandins (PG; PGE_2 & PGI_2) (Nørregaard et al., 2015), estrogen (Baiardi et al., 2005) as well as testosterone (Koshida et al., 1998) in UUO and these parameters may have more effect on renal changes during UUO due to interaction between them and Ang II (Klahr and Morrissey, 2002). This review has focused on the role of the RAS in renal hemodynamic, functional, histological and molecular changes in the kidney with UUO and its interactions with the main vasodilator and vasoconstrictor factors and the main sexual hormones in the obstructive kidney.

RAS arms and ipsilateral kidney alteration in UUO

RAS is considered as an endocrine cascade and has an important role in renal disease (Robles et al., 2014). Renin breaks angiotensinogen (Agt) and converts it to angiotensin I (Ang I) and then the angiotensin-converting enzyme (ACE) breaks Ang I to Ang II. Ang II is one the main arms of RAS and enforces its activity via AT_1R and AT_2R (Yoon and

Choi, 2014). The classical RAS in the kidneys (ACE/Ang II/AT_1R axis) enhances vasoconstriction, inflammation and oxidative stress through activation of NADPH oxidase enzyme, water and salt retention, proliferation of cell and increases the generation of reactive oxidative species (ROS) and fibrosis (Zhong et al., 2011). Ang II also increases the expression of many mediators such as basic fibroblast growth factor, transforming growth factor-beta1 (TGF-β1), platelet-derived growth factor (PDGF), osteopontin (OPN), vascular cell adhesion molecule-1 (VCAM-1), tumor necrosis factor-alpha (TNF-α), and nuclear factor kappa-B (NF-kB) (Fig. 1) (Zhong et al., 2011). The other important arm of RAS is Ang 1-7 (Chappell, 2012). The renal protective effect of Ang 1-7 is created with bind to MasR and its activation (Mansoori et al., 2014). It is demonstrated that MasR crosstalks with Ang II receptors, and AT_1R and AT_2R antagonists inhibit some actions of Ang 1-7 (Mansoori et al., 2014). Water and salt regulation and tubular function are affected by crosstalk mechanisms between AT_1R and AT_2R with Ang 1-7 (de Castro et al., 2005). Moreover, the AT_2R and MasR have a renoprotective effect (Villela et al., 2015). The ACE/Ang II/AT_1R axis has proliferative and fibrogenic actions and ACE2/Ang 1–7/MasR axis acts as an anti-proliferative and anti-fibrogenic arm of RAS and the function of these arms is against each other (Iwai and Horiuchi, 2009). The Kidney levels of Ang II and Ang 1-7 are balanced with ACE and ACE2 function (Chappel and Ferrario, 2006). Consistent with this issue, it is known that ACE2 has a renoprotective role in UUO (Liu et al., 2012). The important role of RAS in UUO has been demonstrated (Klahr and Morrissey, 2002). UUO model induced kidney podocyte injury, and then the local elevation of Ang II occurred (Chevalier et al., 2009). After the progression of podocyte injury, a large volume of plasma Agt is infiltrated into the nephrons tubular space and then it was reabsorbed through megalin from proximal tubule and converted to Ang II in proximal tubular cells (Okabe et al., 2015). Thus, the injury increases intrarenal Ang II and the increased Ang II promotes kidney injury due to creating a vicious circle (Fig. 1) (Matsusaka et al., 2012). In addition, RAS is the main effector in renal fibrosis and this impairment increases both tissue and plasma levels of Ang II (Navar, 2014). Ang II increases the production of fibrogenic factors which are known as powerful mediators in renal fibrosis by regulating the release of TGF-β and promotion of the inflammatory process in UUO model (Fig. 1) (Burns et al., 2010). Ang II via AT_1R constricts renal arterioles and causes kidney injury (Fig. 1) (Shin et al., 2005) and moreover the intrarenal elevated level of Ang II induces chronic kidney diseases (Shin et al., 2005). In this regard, it has been shown that the ACE inhibitors and Ang II antagonists decrease the intrarenal Ang II concentration and attenuate the progression of renal injury in UUO and other kidney diseases (Ng et al., 2013). It has been reported that the AT_1R antagonists improved the renal fibrosis in rats with UUO (Wamsley-Davis et al., 2004). Furthermore, circulating renin and prorenin can induce renal fibrosis via different receptor other than AT_1R (Ichihara et al., 2006). Therefore, it seems that renin blockers would be helpful in obstructive kidney injury (Fisher et al., 2008). On the other hand, Ang 1-7 via MasR also attenuates renal fibrosis, oxidative stress, inflammation, and apoptosis in kidney with UUO, and AT_2R knockout rats had a higher mortality rate in UUO (Benndorf et al., 2009).

Accordingly, UUO alters the main arms of RAS as main effectors in renal tissue but subsequently increases the local and plasma levels of Ang II and decreases the levels of Ang 1-7 in the ipsilateral kidney. Generally, UUO via activation of the ACE/Ang II/AT_1R axis and inhibition of the ACE2/Ang 1–7/MasR axis induces ipsilateral kidney injury.

RAS arms and ipsilateral kidney alteration in UUO

The RAS induces both renal structural and functional alterations in the kidney suffering from UUO, and the intensity of damage depends on the duration and severity of ureteral obstruction (Manucha, 2007). From hemodynamics view, renal blood flow (RBF) and ureteral pressure alter in different stages after UUO. It was reported that RBF is initially increased during the first hour after obstruction and then returns to baseline by 5 hours and is finally decreased to 40% in 17 hours later (Felsen et al., 2003). As the final stage, RAS and sympathetic nervous system are the main effectors for afferent arteriolar constriction in UUO model (Fig. 1) (Felsen et al., 2003). Inhibition of ACE or Ang II actions maintain the RBF to attenuate renal disturbance (Hvistendahl et al., 2002). The low dose injection of Ang II increases glomerular filtration rate (GFR) after removal occlusion in rat with UUO,

because removal occlusion mainly induces the down-regulation of the AT_1R in the afferent arteriole (Helou et al., 2003). This change is related to the RAS activation during UUO (Bae et al., 2007). In this regard, it has been observed that administration of AT_1R antagonist increases both RBF and GFR in the kidney with UUO (Topcu et al., 2007) while this finding was confirmed by other studies that candesartan as AT_1R blocker could attenuate the GFR reduction in the kidney with UUO (Topcu et al., 2007). Moreover, UUO downregulates the gene expression of sodium and aquaporin-2 transporters in renal nephrons and AT_1R antagonist reverses this trend (Topcu et al., 2007). It also has been found that endogenously activated AT_1R is the main mechanism to inhibit H^+ secretion at the collecting tubule just in early hours after occlusion removal in kidney suffering from UUO (Gheitasi and Moosavi, 2014).

UUO induces renal histological changes after a short time. It causes medullary and cortical tubular atrophy after 10 days post obstruction and increases the relative volume of the ipsilateral kidney (Cochrane et al., 2005). Ang II increases the expression of many factors, such as TNF-α, TGF-β1 (Misseri et al., 2005), NF-kB, intercellular adhesion molecule-1, PDGF, monocyte chemotactic protein-1, insulin-like growth factor and VCAM-1 in obstructive nephropathy (Klahr, 2001). Ang II and TGF-β1 have a central role in renal fibrogenesis (Fig. 1) and AT_1R is the powerful Ang II receptor involved in renal interstitial fibrotic response (Brewster and Perazella, 2004). To confirm this fact, it has been shown that macrophage infiltration, collagen deposition and alpha-smooth muscle actin (α-SMA), collagen IV and fibroblast expression were decreased in AT_1R knockout rats after UUO (Figure 1) (Guo et al., 2001). In addition, Ang II increases the expression of Bax (Bcl2 associated X, apoptosis regulator) protein via AT_1R and then activates caspase-3 cascade and finally induces apoptosis in the kidney with UUO (Bhaskaran et al., 2003). Accordingly, Ang II as one of the RAS arms increases α-SMA and TGF-β expression in the kidneys (Burns et al., 2010). Also, the expression of α-SMA and fibrogenic cytokines (TGF-β1 and TNF-α) increases after UUO prolongation and induces interstitial fibrosis (Iwano et al., 2002). On the other hand inhibition of RAS decreases OPN, monocyte chemoattractant protein-1 and macrophage infiltration in renal interstitial tissue in the kidney injury models (Fig. 1) (Amann et al., 2003). There is controversial data that AT_2R blockade (but not the AT_1R blockade) decreases macrophage infiltration in ipsilateral UUO kidney (Esteban et al., 2004). However, another report concludes that AT_1R antagonist reduced the expression of small mothers against decapentaplegic-2 (Smad2) protein in the kidney with UUO and therefore it attenuates the tubulointerstitial fibrosis in the ipsilateral kidney (Wamsley-Davis et al., 2004). In addition, there is a significant correlation between the Agt gene expression and the severity of kidney injury in UUO model (Guo et al., 2001). On the other hand, AT_2R attenuates the accumulation of the renal interstitial collagen after UUO (Hashimoto et al., 2004) and consistent with this observation, interstitial fibrosis increases in the AT_2R knockout UUO mice (Chow et al., 2014). Also, Ang 1-7 as another arm of RAS, inhibits the TGF-β1/Smad signaling and AT_1R expression in obstructive nephropathy and then attenuated the renal fibrosis and apoptosis (Kim et al., 2015). However, in UUO rats with loss of ACE2, it has been found that NF-kB and TGF-β1/ Smad signaling mediated by Ang II increases and then induces inflammation and renal fibrosis (Trachtman et al., 2004). Therefore, ACE2 elevation can decrease Ang II-induced Smad ubiquitin regulatory factors 2 dependent ubiquitin degradation and TGF-β1/Smad-mediated renal fibrosis in mice suffering from UUO nephropathy (Liu et al., 2012). The expression of catalase, superoxide dismutase and glutathione peroxidase enzymes decrease in kidney with UUO (Yeh et al., 2011) and also their activity is decreased with prolonged UUO (Sunami et al., 2004). Elevated levels of Ang II induce cytokines production and downregulate the antioxidant enzymes transcription in ipsilateral obstructed kidney and these changes induce renal oxidative stress after UUO (Klahr, 2001). Therefore, UUO reduces RBF both directly and by stimulating and increasing the Ang II level (Fig. 1). Both renal hemodynamic and functional impairment and also increased levels of Ang II will promote to complete a vicious cycle in obstructed kidney. Consequently, these disorders induce the activation of inflammatory factors and cytokines in the ipsilateral kidney with UUO and its outcome leads to renal fibrosis, apoptosis and kidney injury (Fig. 1).

RAS interactions with vasodilators and vasoconstrictors mediators and sexual hormones

in UUO

NO acts against of Ang II and compensates the

Table 1: RAS interactions with the main vasodilators and vasoconstrictors mediators and sexual hormones in UUO.

Table 1. Interacions in kidney with UUO	*Ang II*	*Ang 1-7*
Nitric oxide	- NO increased via Ang II binding AT_2R mechanism (Carey et al., 2000). - NO acts against of Ang II (Ito et al., 2005).	- Ang 1-7 stimulates the gene expression of NO (Heitsch et al., 2001).
Endothelin	- Ang II and ET-1 crosstalk increases the renal fibrosis (Bae et al., 2007). - Ang II stimulates the renal ET-1 expression (Bae et al., 2007). - Ang II can decrease RBF via ET_AR (Schneider et al., 2007; Hammad et al., 2014).	
Vasopressin	-Ang II via AT_1R upregulates the V_1R expression in tubules (Wong and Tsui, 2003).	
Prostaglandins	- Ang II via AT_1R increases the PGE_2 secretion (Manucha et al., 2004; Jensen et al., 2006).	- Ang 1-7 stimulates the PGI_2 and cAMP production (Tallant and Clark, 2003; Pinheiro and Simões e Silva, 2012).
Bradykinin	- Bradykinin increased via Ang II binding AT_2R mechanism (Schanstra et al., 2002). -AT_1R has crosstalk with the B_1R in renal fibrosis (Huart et al., 2015).	- Ang 1-7 increases the bradykinin gene expression (dos Santos et al., 2001). - The MasR and B_2R crosstalk have an antifibrotic effect (dos Santos et al., 2001).
Natruretic peptide	- ANP has a renoprotective role against Ang II effects (Bae et al., 2007).	
Adenosine	- Ang II increases the adenosine-induced renal fibrosis (Roberts et al., 2014). -Ang II contributes directly to renal fibrosis via $A_{2B}R$ activation (Dai et al., 2011). - Adenosine via A_2R acts against of Ang II (Carlström et al., 2008a).	
Sexual hormons	- Estrogen exerts its renoprotective effects via up-regulation of AT_2R (Cho et al.). - Testosterone via Ang II increasing level induces renal injury (Metcalfe et al., 2008).	

UUO: Unilateral ureteral obstruction, Ang II: Angiotensin II, Ang 1-7: Angiotensin 1-7, NO: Nitric oxide, AT_2R: Angiotensin receptor subtype 2, ET-1: Endothelin subtype 1, ET_AR: Endothelin receptor subtype A, AT_1R: Angiotensin receptor subtype 1, PGE2: Prostaglandin E2, PGI2: Prostaglandin I2, cAMP: Cyclic adenosine monophosphate, B_1R: Bradykinin receptor subtype 1, MasR: Angiotensin 1-7 receptor, B_2R: Bradykinin receptor subtype 2, ANP: Atrial natriuretic peptide, A_2R: Adenosine receptor subtype 2.

Nitric oxide (NO) & RAS in UUO

It is known that NO effects the renal hemodynamics in the early phase of acute UUO (Schulsinger et al., 1997) and acts as an antifibrotic factor in chronic UUO (Morrissey et al., 1996). Nevertheless, it has been shown that renoprotective effects of NO are less important in bilateral ureteral obstruction rather than UUO (Tirani et al., 2015). However, during UUO, vasodilator system and improves the renal injury (Ito et al., 2005). There is an interesting communication between AT_2R and NO (Carey et al., 2000). During Ang II elevation, this peptide stimulates the vasodilator cascade mechanism via AT_2R and then activates the enzymes that involve in the production of the bradykinin and NO (Table 1) (Carey et al., 2000). Palm et al. (2008) showed that the expression

of Ang II, AT_2R and NO proteins increase in the kidney clipped of early Goldblatt hypertensive rats and these changes maintain the oxygen availability in a kidney with reduced perfusion pressure. Also, there is a complex interaction among Ang II, NO, and adenosine with TGF-β1 mechanism pathway in renal vessels (Schnermann and Levine, 2003). Therefore, NO is a considerable physiological mediator that increased via Ang II binding AT_2R mechanism (Carey et al., 2000; Palm et al., 2008; Yayama and Okamoto, 2008). In addition, Ang II mediates AT_1R vasoconstriction mechanism that acts versus local NO in kidney (Table 1) (Patzak et al., 2001). Studies have shown that Ang 1-7 stimulates the gene expression of NO (Heitsch et al., 2001) and bradykinin (dos Santos et al., 2001). Hence Ang 1-7 may limit the proliferative effect of Ang II through the NO cascade mechanism in kidney suffering from UUO (Su et al., 2006). Animal studies have shown that renal injury could be decreased in UUO with NO supplementation (Alan et al., 2016; Felsen et al., 2003; Sun et al., 2012). This attenuation in renal injury can be achieved either by NOS activating which elevates NO formation (Felsen et al., 2003). Moreover, increase in NO production can involve the Ang 1-7 function mechanisms in renal injury (Table 1) (Campbell, 2003; Fernandes et al., 2001).

Endothelin & RAS in UUO

In the kidney, endothelin (ET) receptor (ETR) blockade inhibits the vasoconstrictor effect of Ang II (Riggleman et al., 2001; Wenzel et al., 2001). Actually, it is most likely that the ETR antagonist ability to inhibit the Ang II actions is due to the Ang II-dependent release of ET-1 from the vascular endothelium (Kohan et al., 2011). Moreover, it has been shown that the endothelin receptor subtype A (ET_AR) is located on vascular muscle and its activation causes vasoconstriction, whereas ET_BR is located on the endothelial cell membrane and its activation causes production of NO from endothelial cells to counteract vasoconstriction of ET_AR (Frommer and Müller-Ladner, 2008; Schneider et al., 2007). Also, the heterodimerization of ET_AR with AT_1R may form interplay in post-receptor signaling (Hammad et al., 2014). Apparently different kinds of endothelins are important agents to elicit Ang II associated changes (fall in RBF and GFR, then down-regulation of the afferent arteriolar AT_1R) (Hammad et al., 2014). During UUO, blockade of the ET_AR/ET_BR may prevent some events leading to change in function of the intrarenal RAS and endothelin system (Hammad et al., 2014). It has been shown that Ang II can directly stimulate the renal ET-1 expression in mesangial and glomerular endothelial cells and also increased ET-1 expression may be created by the enhanced local RAS activation in the obstructed kidney (Table 1) (Bae et al., 2007). In this regard, it was reported that in the chronic phase of UUO, ACE and ET-1 mRNA expression were increased while ACE2 was decreased which contributes to increasing the expression of TGF-β1 in the ipsilateral obstructed kidney in rats (Bae et al., 2007). Both Ang II and ET-1 contribute in vasoconstriction and involve in the interstitial inflammatory response, tubular cell apoptosis as well as fibrosis in the kidney (Table 1) (Esteban et al., 2004; Hegarty et al., 2003; Moridaira et al., 2003). To support of this observation, it is demonstrated that alteration of intrarenal pressure in obstructed kidney causes the mechanical stretch in tubular cells, that releases some mediators (inflammatory, lethal and profibrotic) such as TGF-β1 and ET-1 which exacerbates kidney injury (Fig. 1) (Miyajima et al., 2000).

Vasopressin & RAS in UUO

Ang II stimulates the expression of inner medullary collecting ducts vasopressin 2 receptor (V_2R) in UUO model and regulates the abundance and localization of vasopressin-regulated transport proteins in the kidney (Wong and Tsui, 2002; Wong and Tsui, 2003). AT_1R blockade reduces the vasopressin-resistant polyuria and prevents from down-regulation of the vasopressin-regulated aquaporin-2 (AQP2) and Na^+-K^+-$2Cl^-$ transporter in the post-obstructive kidney (Jensen et al., 2006). AT_1R antagonist also reduces down-regulation of inner medulla V_2R in the post-obstructive kidney in UUO (Harris and Young, 1977; Reilly et al., 1995). This paradoxical effects of Ang II on the tubular properties of fluid transport could be caused by a biphasic response to the different concentration of Ang II (Harris and Young, 1977; Reilly et al., 1995). So that Ang II stimulates fluid transport at low physiological concentration, whereas high and pharmacological dose inhibits it as seen in UUO (Horita et al., 2002). It was observed that blockade of AT_1R in post-obstructive kidney inhibits

down-regulation of the V_2R and AQP2 (Jensen et al., 2009), however, the influence of Ang II on the V_2R complex proteins and regulation AQP2 intracellular pathway aren't determined up to now (Jensen et al., 2009). AT_1R has significant effects on AQP2 and in this regard, it was observed that AT_1R blockade decreases the AQP2 and AQP1 expression in arginine vasopressin treated rats (Table 1) (Kwon et al., 2005).

Prostaglandins, Bradykinin & RAS in UUO

It has been shown that there is an interaction between Agt and PG systems in the obstructed kidney (Manucha et al., 2004). The renal generation of PGE2 increased due to overexpression of inducible enzyme cyclooxygenase-2 (COX2) in UUO (Nørregaard et al., 2005; Okegawa et al., 1983). Inhibition of Ang II prevents the increased secretion of eicosanoids and reduces renal COX2 expression in post-obstructive kidney (Manucha et al., 2004). It is revealed that AT_1R antagonist attenuates the induction of COX2 and thereby this treatment reduces PGE2 generation in kidney suffering from UUO (Jensen et al., 2006). Therefore, renal medullary COX2 up-regulation may be inhibited by AT_1R antagonists in the UUO adult rat (Coleman et al., 2007). In addition, Ang 1-7 inhibitory effects on vascular and cellular growth mechanisms (antiproliferative action) exerted through stimulation of PGI_2 and cyclic adenosine monophosphate production as well the inhibition of mitogen-activated protein kinases (Table 1) (Pinheiro and Simões e Silva, 2012; Tallant and Clark, 2003). The protective role of Ang 1-7 in renal fibrosis remains speculative; however, some findings in MasR genetic deletion animals support it (Pinheiro et al., 2009). It has been reported that ACE has a higher affinity for bradykinin than Ang I (Jaspard et al., 1993). ACE degrades bradykinin (Ceravolo et al., 2014) and its inhibition increases bradykinin levels significantly (Su, 2014). In the UUO model, the blockade of the bradykinin B_1 receptor (B_1R) had a curative effect as antifibrotic (Klein et al., 2009; Klein et al., 2010) and also bradykinin B_2 receptor (B_2R) stimulation reduces tubule-interstitial fibrosis induced by UUO (Schanstra et al., 2002). These observations reveal the potential role of bradykinin in present of antifibrotic effects of ACE inhibitors (Schanstra et al., 2002). The B_1R antagonist may be considered as the gold standard of AT_1R antagonist (Huart et al., 2015) and the additive antifibrotic effects of B_1R and AT_1R antagonists simultaneously are reported (Huart et al., 2015). Actually, it seems that a co-therapy of AT_1R and B_1R could be much more effective to decelerate the progression of renal fibrosis (Table 1).

Atrial natriuretic peptide & RAS in UUO

The activity of ANP system was enhanced in UUO kidney which may partially compensate against progressive renal fibrosis in chronic UUO (Bae et al., 2007). The increased expression of ANP in post-obstructed kidney supports this idea that ANP has a protective role against UUO (Kim et al., 2001; Kim et al., 2002). The increased ANP synthesis may also have a role in enhanced urinary Na^+ excretion against the extracellular fluid volume expansion in the UUO kidney (Bae et al., 2007). It is reported that ANP system was increased in the acute and chronic phase of UUO model in obstructed kidney (Bae et al., 2007). Even in chronic stages of obstructive uropathy, it is suggested that the local ANP synthesis may play a role to compensate against progressive renal disease (Table 1) (Bae et al., 2007).

Adenosine & RAS in UUO

Renovascular response to adenosine is absolutely different in hydronephrotic mice (Carlström et al., 2008a). Activation of adenosine receptor 2B ($A_{2B}R$) in both Ang II-infused mice and UUO mice promoted renal fibrosis (Roberts et al., 2014; Xiao et al., 2013). while interleukin-6 (IL-6) as a common profibrotic signaling molecule is responsive for adenosine-mediated renal fibrosis by induction procollagen gene expression via $A_{2B}R$ activation (Dai et al., 2011). Actually increased adenosine-induced by Ang II plays a substantial role in renal fibrosis and renal dysfunction and it also contributes directly to renal fibrosis via $A_{2B}R$ activation (Table 1) (Dai et al., 2011; Roberts et al., 2014). To confirm these observations, it has been shown that the effect of chronically elevated adenosine via $A_{2B}R$ signaling mechanism on kidney fibrosis in UUO mice infused with Ang II is related to local effects of adenosine as well as its systemic actions (Dai et al., 2011). Also, there is a complex interaction among NO, adenosine and Ang II on vascular resistance in obstructed kidney (Schnermann and Levine, 2003). Adenosine and Ang II interact via calcium-dependent/independent

pathways on afferent arteriole (AAs) (Hansen et al., 2007; Lai et al., 2006a). Low levels of adenosine via predominant action on adenosine receptor 1 (A_1R) increase the AA response to Ang II (Lai et al., 2006b) and also high levels of adenosine increase the Ang II response via activating dilatory A_2R in the renal hydronephrotic induced UUO (Table 1) (Carlström et al., 2008b). A reduced dilatory can be created via A_2R in hydronephrotic AAs or increased constrictor can be presented via A_1R mediation (Carlström et al., 2008b).

Sexual hormones & RAS in UUO

Estrogen has renoprotective effect in UUO (Frokiaer and Sorensen, 1995) and RAS is one of the mechanisms by which estrogen exerts its protective effects (Armando et al., 2002; Baiardi et al., 2005). Estrogen can exert its protective effects via up-regulation of AT_2R and Agt but also via down-regulation of renin, ACE and Ang II (Baiardi et al., 2005). In consistent with these studies, it has been seen that estrogen attenuates the renal fibrosis in UUO via increasing the AT_2R expression mechanisms in renal inner medulla and Bowman capsule (Table 1) (Armando et al., 2002; Cho et al. 2011). Moreover, estrogen can induce protective vascular effects via NO mechanism (Mao et al., 2014; Thompson and Khalil, 2003) and reduces the TGF-β1, fibrosis and apoptosis induced by RAS (Dubey et al., 2002; Maric et al., 2004; Matsuda et al., 2001). Experimental evidence suggests that testosterone induces the cell apoptosis and fibrosis in the kidney with UUO (Metcalfe et al., 2008) and ACE inhibitors can reduce the plasma testosterone levels (Koshida et al., 1998). Also, testosterone increases the levels of Ang II which leads to renal vasoconstriction and renal injury (Table 1) (Metcalfe et al., 2008).

It seems that UUO faces the ipsilateral kidney with new challenges, and also alters the expression of most receptors. Furthermore, RAS has interaction with many factors such as PG bradykinin, ANP, NO, adenosine, ET, vasopressin, testosterone and estrogen in the kidney. Since the expression of these factors and their receptors were altered after UUO hence the equations for the ipsilateral kidney will be complex for the return to normal state. Generally NO, ANP, estrogen, bradykinin (via B_2R) and vasodilatory arms of RAS (Ang 1-7 via MasR and Ang II via AT_2R) have renoprotective effects on the ipsilateral kidney with UUO and vice versa vasopressin, endothelin, testosterone, adenosine (via $A_{2B}R$ activation), Ang II (via AT_1R) and bradykinin (via B_1R) intensify the obstructed kidney conditions.

Conclusion

In summary, UUO increases the expression of ACE, Ang II as well as AT_1R and also it decreases the expression of ACE2, Ang 1-7, MasR and AT_2R in the ipsilateral kidney. The decrease of RBF and GFR observed in the obstructed kidney and elevated levels of Ang II exacerbate these disturbances. Moreover, Ang II via AT_1R induces renal fibrosis and apoptosis in the kidney with UUO. AT_2R and MasR play a renoprotective role and attenuate renal fibrosis in UUO model. Moreover, RAS has interaction with the main vasoconstrictor factors such as endothelin, vasopressin and also with the main vasodilator factors such as bradykinin, prostaglandins E2 and I2, NO, ANP and adenosine and the main sexual hormones such as estrogen and testosterone in the obstructed kidney. Finally, the RAS interaction with these factors can change the complex equations to a suitable or critical condition.

Acknowledgments

This research was supported by Isfahan University of Medical Sciences. (Grant # 395353).

Conflict of interest

No conflict of interest was declared.

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