Angiotensin II type 2 receptors in the kidney: evidence for endothelial-cell-mediated renal vasodilatation

Shuji Arima and Sadayoshi Ito

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan

Introduction

Angiotensin II (Ang II), the physiologically active component of the renin–angiotensin system, plays an important role in the regulation of the cardiovascular and renal systems. Based on their different pharmacological and biochemical properties, two distinct subtypes of Ang II receptor have been defined and designated as type 1 (AT₁) and type 2 (AT₂) receptors. While both AT₁ and AT₂ receptors belong to the seven-transmembrane, G-protein-coupled receptor family, the function and signalling mechanism of these receptor subtypes are quite different [1,2]. Extensive pharmacological evidence indicates that most of the well-characterized actions of Ang II (such as vasoconstriction, cell proliferation, and renal salt retention) are now generally considered to result from stimulation of AT₁ receptors [1,2], whereas the functional role of AT₂ receptor has not been well defined. However, recent studies suggest that the AT₂ receptors exert the opposite effects of AT₁ receptors in terms of cardiovascular haemodynamics and cell growth. For example, the activation of AT₂ receptors exerts antigrowth, anti-hypertrophic, proapoptotic [3], and hypotensive effects [4]. In the kidney, activation of the AT₂ receptor has been reported to regulate pressure-natriuresis [5] and to stimulate the production of nitric oxide (NO) and bradykinin [6–8], which may cause renal vasodilatation. We have also demonstrated that in the renal microvasculature activation of AT₂ receptor causes endothelium-dependent vasodilatation, which modulates the vasoconstrictor action mediated by the AT₁ receptor [9]. In this article, we will summarize results obtained from recent studies on the AT₂ receptor-mediated action of Ang II in the kidney, together with other relevant literature. Only a limited number of references are given.

AT₂-receptor-mediated action of Ang II in the kidney

The renal distribution of the AT₂ receptor and its mRNA shows remarkable species differences and is most prominent in fetal and newborn mammalian kidneys. High levels of AT₂ receptors and mRNA expression have been demonstrated in the macula densa of ovine fetal kidney, suggesting a potential role of AT₂ receptors in the development of this structure [10]. Nishimura et al. [11] also reported the involvement of AT₂ receptors in the formation of the embryonic ureter by the promotion of the mesenchymal cell apoptosis. In contrast, the expression of AT₂ receptors in the adult mammalian kidney has been reported to be very low, and localized mainly in the glomerular mesangial cells [12,13] or adventitia of the preglomerular arcuate and interlobular arteries [14]. However, recent functional studies have demonstrated that some part of the Ang II action on the kidney is mediated by AT₂ receptors. Using a microdialysis technique, Siragy and Carey [6,7] have demonstrated that the renal AT₂ receptors may be activated during sodium depletion or Ang II administration in the conscious adult rat and that the AT₂ receptor mediates renal interstitial production of NO and bradykinin, leading to increased cGMP levels in the renal interstitial fluid. In addition, studying with adult AT₂ receptor-null mutant mice, they found that the AT₂ receptor plays a counter-regulatory protective role against the AT₁ receptor-mediated antinatriuretic and pressor actions of Ang II and that this protective action of the AT₂ receptor is mediated by bradykinin and NO [8]. They also found that the AT₂ receptor decreases renal interstitial prostaglandin E₂ (PGE₂) level by stimulating its conversion to PGF₂α by 9-ketoreductase [6,15].

These observations suggest that the renal AT₂ receptor may be re-expressed in the adult kidney in response to Ang II and may mediate renal vasodilatation and/or inhibition of tubular sodium reabsorption by stimulating bradykinin, NO, and/or eicosanoid production. However, a potential renal tubular action of the AT₂ receptor is still controversial. Lo et al. [16] isolated tubular function from haemodynamic action by maintaining a constant renal blood flow and found that blockade of the AT₂ receptor markedly and rapidly increased diuresis and natriuresis from the rat kidney. Madrid et al. [5] also observed that activation of the NO/cGMP system by AT₂ receptor impaired pressure diuresis. These studies indicate the possibility of renal sodium retention by AT₂ receptors. In marked contrast, Haithcock et al. [17] recently demonstrated that the
proximal tubular AT$_2$ receptor is linked to inhibition of bicarbonate reabsorption, an effect that opposes AT$_1$ receptor-mediated facilitation of sodium and bicarbonate reabsorption. Further studies examining the tubular action of AT$_2$ receptor (whether natriuretic or antinatriuretic) are clearly required.

Vasodilator action of AT$_2$ receptors in renal microvessels

Ichiki et al. [4] and Siragy et al. [8] recently demonstrated that AT$_2$ receptor null mutant mice have a higher blood pressure and exert an enhanced pressor response to exogenously infusèd Ang II compared to the wild-type control. In addition, as mentioned above, several studies have demonstrated that the AT$_2$ receptor stimulates bradykinin, NO, and/or eicosanoid production in the kidney. Taken together, these findings suggest that the renal AT$_2$ receptor mediates vasodilation and plays an important role in the control of blood pressure. To test this possibility, we examined whether selective activation of AT$_2$ receptor causes vasodilatation in the afferent arteriole (Af-Art) [9], a vascular segment that accounts for most of the preglomerular resistance. We microperfused rabbit Af-Arts at 60 mmHg in vitro, and examined the effect of Ang II on the luminal diameter.

We found that (i) blockade of AT$_1$ or AT$_2$ receptor abolishes or augments the Ang II-induced vasoconstriction in Af-Arts, respectively; (ii) in preconstricted Af-Arts treated with an AT$_1$ receptor antagonist, Ang II now causes dose-dependent dilatation, which is abolished by AT$_2$ receptor blockade; (iii) the dilatation was unaffected by inhibiting the synthesis of NO or prostaglandins, however, it was completely abolished by either disrupting the endothelium or inhibiting the synthesis of epoxyeicosatrienoic acids (EET).

Our results demonstrate for the first time that in the renal resistance arterioles, activation of the AT$_2$ receptor induces endothelium-dependent and EET-mediated vasodilatation, which modulates the vasoconstrictor action of Ang II-mediated by the AT$_1$ receptor. Figure 1 shows an example of AT$_2$ receptor-mediated dilatation of Af-Art (left) and its blockade by EET synthesis inhibition (right). Similar findings (activation of AT$_2$ receptor induces vasodilatation and modulates the vasoconstrictor action of Ang II mediated by AT$_1$ receptor) were also obtained in the postglomerular efferent arterioles [18], another crucial vascular segment to the control of glomerular haemodynamics.

Our findings that EETs but not NO synthesis inhibition diminishes AT$_2$ receptor-mediated vasodilatation in Af-Arts suggest that activation of AT$_2$ receptor stimulates EETs but not NO release in Af-Arts. This notion is supported by the findings of Thorup et al.
AT and maintenance of hypertension in SHR. 1995; 95: 1394–1397. From these studies, it has now become obvious that impaired function of the AT2 receptor may play an important role in various physiological and pathological conditions. Goto et al. [13] reported that cultured mesangial cells, prepared from stroke-prone spontaneously hypertensive rats (SHRSP), showed lower expression of AT2 receptors and higher proliferation activity as compared to those of normotensive Wistar-Kyoto rats (WKY). This suggests that AT2 receptors may exert an antiproliferative effect in mesangial cells. Consistent with these findings, accelerated renal interstitial fibrosis and collagen deposition has been observed in adult AT2 receptor null mutant mice during unilateral obstruction [22]. In addition, antihypertensive effects of the renal AT2 receptor have also been demonstrated. Siragy and Carey [23] recently demonstrated that the AT2 receptor, by stimulating the renal interstitial release of bradykinin and NO, prevents a further increase in blood pressure in a rat renovascular hypertension model. They also found that in the absence of AT2 receptor, conversion from PGE2 to PGF2α is decreased and that increased vasodilator PGs (PGE2 and PGI2) protect against the development of hypertension [24]. We have also demonstrated that vasoconstrictor action of Ang II is exaggerated in Af-Arts of SHR due to an impaired function of the AT2 receptor before the development of hypertension [25]. Since an exaggerated response of Af-Arts to Ang II is thought to be responsible, at least in part, for the elevated renal vascular resistance (which is important for development and maintenance of hypertension), our findings suggest that impaired function of the AT2 receptor in Af-Arts may play a role in the development and maintenance of hypertension in SHR.

From these studies, it has now become obvious that AT2 receptors play some important roles in the pathogenesis and remodelling of renal and cardiovascular diseases including hypertension. Thus, AT2 receptor antagonists, newly developed and already available antihypertensive drugs, may exert their renoprotective and antihypertensive effects partly through AT2 receptor activation, because treatment with AT2 receptor antagonists elevates plasma levels of Ang II [26], which preferentially binds to AT2 receptor. Further understanding of the renal AT2 receptor function may contribute to new therapeutic strategies of AT2 receptor antagonists for renal diseases and hypertension.

References

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