# $AT_1$ and $AT_2$ Receptor in the Kidney: Role in Health and Disease

By Helmy M. Siragy

**The renin angiotensin system plays an important role in the control of body fluid and electrolyte homeostasis and blood pressure regulation. Angiotensin II is the most effector hormone of this system and functions mainly through stimulation of its subtype receptors, namely, the $AT_1$ and $AT_2$ receptors. Most of the known physiological and pathologic effects of angiotensin II are mediated through stimulation of the $AT_1$ receptor. The knowledge about the involvement of the $AT_2$ receptor in physiological and pathologic processes is still evolving. In the kidney, both the $AT_1$ and $AT_2$ receptors contribute to the regulation of renal hemodynamic and tubular functions. Also, these receptors regulate renal cellular growth and matrix formation. However, $AT_2$ receptor possesses functions that counteract the effects of the $AT_1$ receptor. The balance between the $AT_1$ and $AT_2$ receptors can determine the renal status in health and disease.**



ALL THE COMPONENTS of the renin angiotensin system (RAS) are present within the kidney. Angiotensinogen is present in mesangial and tubular cells, renin in juxtaglomerular cells, and the enzymes responsible for the generation of angiotensin II (Ang II), mainly the angiotensin-converting enzyme (ACE) and chymase in the vascular endothelium and tubular epithelium. Classically (Fig 1), Ang II generation depends on the cleavage of angiotensinogen to angiotensin I by renin, the rate-limiting step. This is followed by the conversion of angiotensin I to Ang II by ACE. However, more recently it has been recognized that other enzymes (Fig 1) constitute active and alternative pathways that lead to local generation of Ang II. Independent of renin, tissue plasminogen activator (t-PA), cathepsin G, and tonin can generate Ang II from angiotensinogen.[1] Similarly, the enzyme chymase can cleave angiotensin I to Ang II independent of ACE.[2] It is estimated that 40% of renal Ang II is formed through these alternative pathway.[3] The majority of locally generated renal Ang II functions as a paracrine hormone with 1000-fold higher levels in the kidney than its systemic plasma levels.[4] Ang II is the principal effector hormone of the RAS.

## THE $AT_1$ RECEPTOR

The cloning of the $AT_1$ receptor[5,6] and development of its specific nonpeptide antagonists[7] advanced our understanding of its function in health and disease. $AT_1$ receptor is a member of the superfamily G protein-coupled receptor[8] and is abundantly distributed in the kidney. It is present in glomerular mesangial cells, proximal and distal tubular epithelia, medullary interstitial cells, and renal vasculature.[9-14] The intracellular signaling system for $AT_1$ receptor is complex and involves G protein coupled and G protein-independent pathways. Binding of Ang II to the $AT_1$ receptor (Fig 2) activates phospholipase C A2 and D,[1,5,6] increases intracellular calcium and inositol 1,4,5-triphosphate levels, activates the mitogen-activated protein kinases, extracellular regulated kinases, and JAK/STAT pathway[15] leading to enhanced protein phosphorylation and stimulation of early growth response genes.[16,17] In addition, $AT_1$ receptor inhibits adenylate cyclase, which attenuates the production of cyclic adenosine 3′, 5′-monophosphate (cAMP). Thus, $AT_1$ receptor increases the cyclooxygenase system activity through phospholipases A2 and D and enhances vasoconstriction through reduction in cAMP and increase in intracellular calcium. These signaling pathways indicate that stimulation of renal $AT_1$ receptor in the kidney causes vasoconstriction, sodium reabsorption, protein synthesis, and cellular growth.[16,17]

## THE $AT_2$ RECEPTOR

$AT_2$ has little similarity to the $AT_1$ receptor structure, tissue expression, signaling, or functions. There is only 32% to 34% amino acid sequence homology between the $AT_1$ and $AT_2$ receptor.[18,19] In the kidney, $AT_2$ receptors are located in vasculature, glomeruli, juxtaglomerular apparatus, tu-

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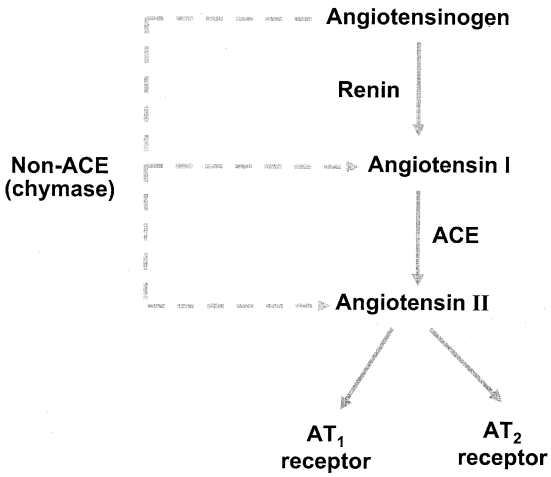


**Fig 1. The renin–angiotensin system cascade.**

bules, afferent arteriole, and renal capsule.[20-23] The signaling mechanisms of the $AT_2$ receptor are not fully elucidated (Fig 3). Although $AT_2$ is a member of superfamily G protein-coupled receptor, it has different signaling mechanisms from those associated with this receptor family. The $AT_2$ receptor signal is mediated by G protein $G_I$ to modulates $K^+$ channel activity,[24] and activates protein–phosphotyrosine phosphatase (PTP), resulting in the reduction of mitogen-activated protein kinase (MAPK) activity and growth inhibition.[25,26] $AT_2$ stimulates mitogen-activated protein kinase phosphatase-1 (MKP-1) and inhibits ERK activity through phosphotyrosine and phosphothreonine.[27,28] In addition, $AT_2$ receptor activates the protein tyrosine phosphatase, SHP-1, to terminate the signaling by cytokine growth factor.[29] Another $AT_2$ receptor signaling pathway is mediated through ceramide production to induce apoptosis.[30,31] In vivo studies demonstrated that stimulation of $AT_2$ receptor increases renal cortical and medullary interstitial bradykinin–nitric oxide cGMP cascade.[32-34] In renal proximal tubule epithelial cells, $AT_2$ receptor signal is linked to a membrane-associated phospholipase A2.[35-37]

## $AT_1$ AND $AT_2$ RECEPTORS AND RENAL DEVELOPMENT

In embryonic kidney, $AT_1$ receptor is expressed in immature and mature glomeruli,[38-42] outer medulla, renal pelvis, and the superior part of the ureter.[39,43] During the early stage of renal development, $AT_2$ receptor mRNA is expressed in the mesenchymal cells of the mesonephros followed by its appearance in interstitial mesenchymes, renal capsule, and inner medulla along the papillary duct and between the collecting ducts. At a later stage of renal development $AT_2$ receptor expression extends to the cortex.[39,40] Absence of the $AT_1$ receptor causes atrophy of renal papilla and pelvis formation.[43-45] In contrast, absence of $AT_2$ receptor does not cause these renal developmental abnormalities.[46,47] After birth mutation of $AT_1$, receptor is associated with hypotension and increased renin and Ang II production.[48] Newborn rats treated with an $AT_1$ receptor blocker developed renal vascular hypertrophy and papillary atrophy.[49-51] Another evidence for the contribution of the $AT_1$ receptor to urinary tract development and function is the development of hydronephrotic lesions in the renal parenchyma, lack of ureteral smooth muscle cells normal proliferation, and absence of renal pelvis peristalsis in mice lacking this receptor.[43]

## RENAL FUNCTION OF THE $AT_1$ RECEPTORS

The distribution of renal $AT_1$ receptor correlates with intrarenal sites of major physiological effects of Ang II in blood vessels, proximal tubules, and glomeruli. Through a short-loop negative feedback mechanism, Ang II suppress renin production

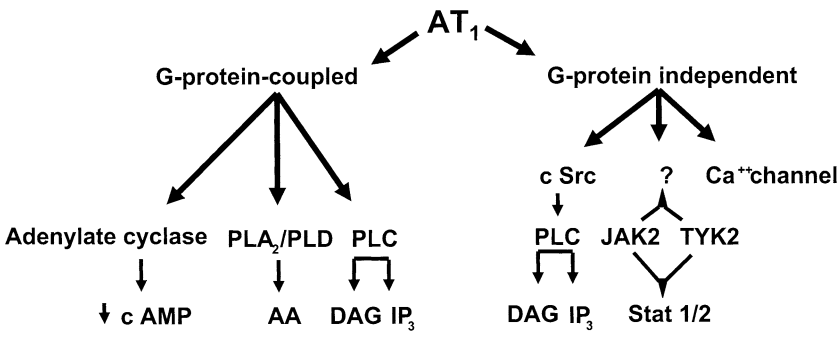


**Fig 2. Angiotensin $AT_1$ receptor signaling pathways.**

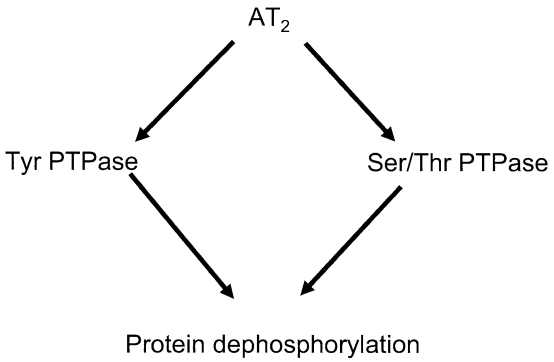


**Fig 3. Angiotensin $AT_2$ receptor signaling pathways.**

through stimulation of $AT_1$ receptor.[52-54] In addition, $AT_1$ receptor enhances renal tubular sodium absorption,[55] reduces renal blood flow, preferentially increases efferent arteriolar resistance and glomerular filtration pressure.[56] Independent of the tubular and hemodynamic effects, $AT_1$ stimulates vascular cell hypertrophy and hyperplasia,[55] reactive oxygen species production,[57] induction of inflammation,[58] thrombosis,[59] and fibrosis.[60]

## RENAL FUNCTIONS OF THE $AT_2$ RECEPTOR

Stimulation of the $AT_2$ receptor leads to generation of bradykinin (Fig 4),[61,62] nitric oxide (Fig 5), and cGMP[32-34] and enhances the activity of 9-ketoreductases enzyme leading to conversion of prostaglandin E2 ($PGE_2$) to prostaglandin $F_{2\alpha\chi}$.[63,64] Mice lacking the $AT_2$ receptor were unable to generate BK, NO, and cGMP in response to sodium depletion or Ang II infusion.[62] Similarly, $AT_2$ receptor blockade with its specific antagonist, PD123319, reduced renal levels of BK, NO, and cGMP.[32-34] The localization of the $AT_2$ receptor in the renal vasculature, glomeruli, and tubules[63] suggests that this receptor contributes to the regulation of renal hemodynamic and tubular functions.[65] In afferent arteriole, $AT_2$ receptor stimulation causes vasodilatation,[66] whereas in renal tubules, it contributes to sodium excretion and pressure natriuresis. In the $AT_2$-null mice, a subpressor dose of Ang II produced antidiuresis and antinatriuresis.[62] Similarly, in normal mice, $AT_2$ receptor blockade inhibits sodium excretion in response to increased renal perfusion pressure.[67] Furthermore, in the proximal tubule, $AT_2$ receptor directly mediates inhibition of bicarbonate reabsorption[68] independent of hemodynamic changes.

## $AT_1$ AND $AT_2$ RECEPTORS AND BLOOD PRESSURE REGULATION

Multiple $AT_1$ and $AT_2$ receptor mechanisms are involved in the regulation of blood pressure. In resistance vessels, stimulation of the $AT_1$ receptors causes sympathetic nerve stimulation and direct vascular smooth muscle cell (VSMC) contraction,[69] growth, and proliferation.[70] These vasoconstrictor effects are partially mediated by enhanced $AT_1$ receptor facilitated $Ca^{2+}$ entry into VSMCs and aldosterone release.[17] The influence of the $AT_1$ receptor stimulation on renal hemodynamic and tubular function leads to fluid and sodium retention and plays a major role in blood pressure elevation.[1] In the early stage of essential hypertension, Ang II contributes to glomerular hyperfiltration that could

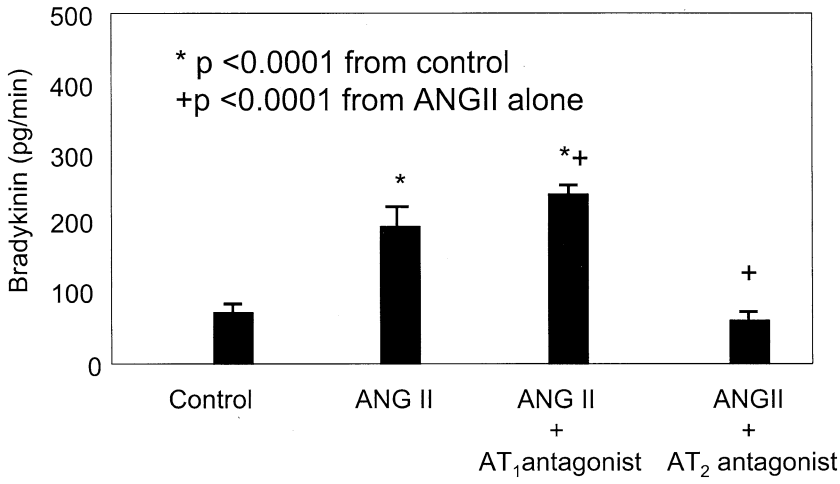


**Fig 4. Tissue bradykinin responses to angiotensin $AT_1$ or $AT_2$ receptor blockade.**

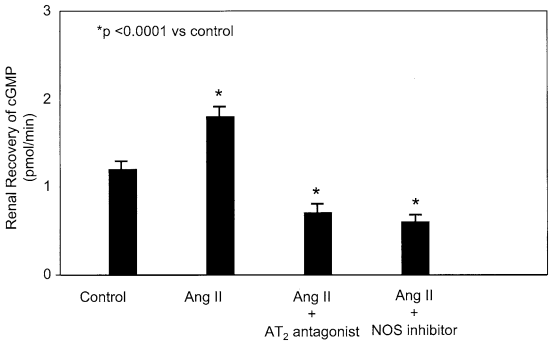


**Fig 5. Angiotensin $AT_2$ receptor mediates generation of NO and cGMP.**

progress to development of nephropathy.[71] These data are supported by the findings of increased sensitivity to the effects of Ang II in the hypertensive state.[72,73] Under normal conditions, $AT_2$ receptor stimulation counteract the vasoconstrictor effects of the $AT_1$ receptors by stimulating a vasodilator cascade mediated by BK-NO-cGMP cascade[32-34] and induction of natriuresis.[62,63,69] Infusion of a subpressor dose of Ang II into mice lacking the gene for the $AT_2$ receptor (Fig 6) produced marked and sustained increase in systolic blood pressure and a reduction in urinary sodium excretion.[62] In this study, the $AT_2$-null mice had low renal levels of BK, NO, and cGMP compared with wild-type animals. Absence of $AT_2$ receptors leave $AT_1$ receptors unopposed and could explain hypersensitivity to Ang II in these animals. Interestingly, animals lacking the $AT_2$ receptors have no or minimally elevated blood pressure at baseline.[47,74] This could be explained by the ability of these animals to increase renal production of vasodilator prostanoids.[64] Treatment with $AT_1$ receptor blockers causes an increase in plasma Ang II levels, which in turn stimulates the $AT_2$ receptor.[75] The blood pressure-lowering effect of the $AT_1$ receptor blockade was abolished by concomitant blockade of the $AT_2$ receptor.[61] In a renovascular hypertension rat model, inhibition of the $AT_2$ receptor attenuated the hypotensive effect of the $AT_1$ receptor blockade.[61] Similarly, the forearm vasodilator response to an $AT_1$ receptor blockade in elderly women was blocked during an $AT_2$ receptor inhibition.[76] These data suggest that the blood pressure-lowering effects of the $AT_1$ receptor blockade are mediated, at least partially, by the $AT_2$ receptor stimulation. More recently, using the $AT_2$ receptor agonist, CGP-42112A, it was shown that this receptor directly induces systemic vasodilator response that is mediated by NO and counterbalances the vasoconstrictor action of the $AT_1$ receptor.[77]

## ROLE OF $AT_1$ AND $AT_2$ RECEPTORS IN RENAL GLOMERULAR AND DIABETIC DISEASES

The beneficial effects of the $AT_1$ receptor blockade in management of diabetic nephropathy suggest that this receptor plays an important role in development of this disease.[78-80] The exact mechanism of the contribution of the $AT_1$ receptor to the development of diabetic nephropathy is not well elucidated. Previous studies demonstrated the influence of diabetes on the RAS. High glucose levels stimulate expression of angiotensinogen gene[81] through synthesis of diacylglycerol and the protein kinase C signal transduction pathway. Also, glucose levels can stimulate angiotensinogen gene through activation of the p38 MSPK signal transduction pathway that is PKC independent.[82] Similarly, kidney rennin mRNA and ACE activities are increased in early streptozotocin (STZ)-induced diabetes in rats.[83] Moreover, hyperglycemia can enhance the expression of the $AT_1$ receptor[84] and reduce the degradation of Ang II by inhibiting Ang II-degrading enzymes,[85] therefore increasing local renal effects of Ang II.[86] Ang II has been shown to stimulate release of several growth factors[87] through the $AT_1$ receptor. Ang II stimulates activation and expression of TGF-$\beta$.[88] Induction of TGF-$\beta$ stimulated renal hypertrophy and accumulation of extracellular matrix proteins

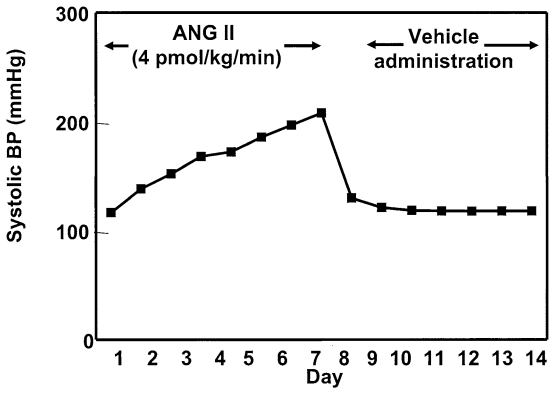


**Fig 6. Mice lacking the $AT_2$ receptor are hypersensitive to subpressor doses of Ang II.**

in the kidney.[89-93] Similarly, cytokines, including TNF-$\alpha$, have been implicated in the development and progression of diabetic nephropathy.[94] TNF-$\alpha$ is stimulated by Ang II and leads to development of renal fibrosis.[95] A recent study of a streptozotocin diabetic rat model demonstrated increased renal production of Ang II and TNF-$\alpha$.[96] $AT_1$ receptor blockade reduced the renal TNF-$\alpha$ levels in these diabetic animals and suggests that this receptor mediates inflammation in diabetes.

In contrast to the $AT_1$ receptor, the potential therapeutic role of the $AT_2$ receptor in diabetic nephropathy is not known. Preliminary reports suggested that Ang II stimulates monocyte chemoattractant protein-1 (MCP-1) expression in cultured mesangial cells.[97,98] MCP-1 is stimulated by nuclear factor-$\kappa$B, whereas the latter is inhibited by NO.[99] Because previous studies showed a reduction in $AT_2$ receptor expression in early-stage diabetic nephropathy,[100] it is expected that MCP-1 transcription is increased in diabetic nephropathy. In hypertensive diabetic rats, the albuminuria and renal histologic changes were associated with a reduction in both $AT_1$ and $AT_2$ receptor gene and protein expression in the kidney.[100] These studies suggest a role for $AT_2$ receptor in development of early changes in diabetic kidney disease, probably through the loss of balance between the $AT_1$ and $AT_2$ receptor activity.

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