Role of the Angiotensin Type 2 Receptor in the Regulation of Blood Pressure and Renal Function

Robert M. Carey, Zhi-Qin Wang, Helmy M. Siragy

Abstract—The renin-angiotensin system is a major physiological regulator of body fluid volume, electrolyte balance, and blood pressure. Virtually all of the biological actions of the principle effector peptide angiotensin II (ANG II) have been attributed to an action at the type 1 (AT₁) ANG receptor. Until recently, the functional role of the type 2 (AT₂) receptor, if any, has been unknown, possibly because the AT₂ receptor has a low degree of expression compared with that of the AT₁ receptor. Evidence has now accumulated that the AT₂ receptor opposes functions mediated by the AT₁ receptor. Whereas the AT₁ receptor stimulates cell proliferation, the AT₂ receptor inhibits proliferation and promotes cell differentiation. These differences in growth responses have been ascribed to different cell signaling pathways in which the AT₁ receptor stimulates protein phosphorylation and the AT₂ receptor dephosphorylation. During the past 5 years, studies have demonstrated that the AT₂ receptor is responsible for vasodilation and natriuresis, thus opposing the vasoconstrictor and antinatriuretic effects of ANG II mediated through the AT₁ receptor. Work from our laboratory and others indicates that the AT₂ receptor stimulates vasodilation and natriuresis by an autocrine cascade including bradykinin, nitric oxide, and cyclic GMP. The AT₂ receptor also has been found to control vasodilator prostaglandins, which have a role in blood pressure regulation. The AT₂ receptor appears to play a counterregulatory protective role in the regulation of blood pressure and sodium excretion that opposes the AT₁ receptor. (Hypertension. 2000;35[part 2]:155-163.)

Key Words: angiotensin II, receptors, angiotensin II, blood pressure, kidney, sodium

The renin-angiotensin system is a major physiological regulator of body fluid volume, electrolyte balance, and blood pressure.¹⁻⁴ However, the mechanisms by which these actions occur remain incompletely understood. The biological actions of angiotensin II (ANG II), the system’s major effector peptide, have been studied for decades and were thought to be mediated by a single ANG II receptor.¹⁻⁴ In the late 1980s, however, the development of highly specific nonpeptide antagonists of the ANG II receptor(s) opened the door to the identification and pharmacological characterization of 2 major receptor subtypes, AT₁ and AT₂.¹⁻⁶ AT₁ receptors were defined as those selectively blocked by biphenylamidazoles such as losartan, whereas AT₂ receptors were defined as those blocked by tetrahydroimidazopyridines, tyipified by PD 123319 (PD).⁵,⁶

In the first half of the 1990s, virtually all of the biological actions of ANG II were characterized by these prototype receptor antagonists as acting through the AT₁ receptor, and the functions of the AT₂ receptor were unknown.¹⁻⁴ More recently, each of these receptors has been cloned and the signal transduction mechanisms for the AT₁ and AT₂ receptors have been clarified.¹⁻⁴,⁷,⁸ We now have available a great deal of information concerning the receptor genes, molecular and protein structures, sites and regulation of expression, and cellular mechanisms of action.

This review will focus on the AT₂ receptor, the physiological function of which was largely unclear until approximately 4 years ago, when studies began to elucidate novel physiological actions of ANG II at the AT₂ receptor.⁹ In this review, we will emphasize the actions of ANG II mediated by the AT₂ receptor that influence blood pressure and renal function. The physiological actions of ANG II at the AT₂ receptor have been difficult to elicit, at least in part because the AT₂ receptor has a low degree of expression in many organs, tissues, and cell types compared with that of AT₁ receptors.¹⁰⁻¹⁶ However, it is now clear that although the AT₂ receptor is highly expressed in fetal life and declines rapidly after birth, the receptor is expressed in the adult and participates in physiological regulation.¹⁷,¹⁸ The AT₂ receptor also is reexpressed in response to injury.

General Considerations of AT₂ Receptors

The molecular structure of the AT₂ receptor resembles that of the superfamily of G-protein–coupled receptors containing 7 transmembrane regions.⁷⁻¹⁹ The cDNA for the AT₂ receptor encodes a 363–amino acid protein (Figure 1), with a molecular weight of 41 220 Da. The AT₂ receptor shares only ≈34% sequence homology with the AT₁ receptor.²⁰ The gene for the AT₂ receptor resides on the X-chromosome and has 3 exons with the entire coding region on the third exon.²⁰
Promoter activity of the rat AT2 receptor gene is regulated by a number of cis-regulator domains.\textsuperscript{20} The AT2 receptor protein contains 5 potential glycosylation sites in its extracellular N-terminal tail. Among the many differences in amino acid sequence, the AT2 receptor but not the AT1 receptor has a conserved LYS\textsuperscript{199}, which is important in ligand-receptor interactions. In addition, there is a potential protein kinase-C phosphorylation site in the second intracellular loop and there are 3 consensus sequences for phosphorylation by protein kinase-C and 1 phosphorylation site by cyclic AMP (cAMP)-dependent protein kinase in the C-terminal cytoplasmic tail of the receptor.\textsuperscript{2}

The signal transduction mechanisms for the AT2 receptor are still not well defined. The growth-inhibitory effects of the AT2 receptor are at least partially mediated by the activation of phosphotyrosine phosphatase, resulting in the inactivation of mitogen-activated protein (MAP) kinase, especially p 42 and p 44 MAP kinases, termed extracellular signal–regulated kinases (ERK).\textsuperscript{8,21–24}

With respect to G-protein coupling, the data remain incomplete. Pertussis toxin attenuated AT2 receptor–mediated inhibition of ERK activity, which suggests that Gi is involved in AT2 receptor cell signaling.\textsuperscript{24} In a study of whole rat fetus, antibodies specific for Gi\textsubscript{a} cosellected AT2 receptor binding sites in a heterogeneous mixture of cell membranes.\textsuperscript{25} Also, transfection of the synthetic third intracellular loop peptide of the AT2 receptor into rat aortic vascular smooth muscle cells resulted in ERK inactivation, growth inhibition, and immunoprecipitation of the third loop peptide with anti-Gi\textsubscript{a} antibody.\textsuperscript{22} Evidence for G-protein coupling also has come from studies in neuronal cells demonstrating that the AT2 receptor activates Gi in the modulation of K\textsuperscript{+} channels.\textsuperscript{26,27} AT2 receptors also activate MAP kinase phosphatase-1 and SHP-1 tyrosine phosphatase, a soluble tyrosine phosphatase.\textsuperscript{28} In addition, in the proximal renal tubule, AT2 receptors appear to be linked to phospholipase A\textsubscript{2} (PLA\textsubscript{2}).\textsuperscript{29}

Altogether, the evidence suggests that the AT2 receptor may be coupled to G-proteins and that the third intracellular loop may be linked with the cell signaling pathway involving G\textsubscript{i} and ERK inactivation. However, activation of G-proteins in cell membranes by the agonist ANG II has not yet been demonstrated for the AT2 receptor, and much further work is required to define the cell signaling pathways of the receptor.

**AT2 Receptor Expression and Regulation**

The AT2 receptor is widely expressed in fetal tissues, but in almost all tissues there is rapid regression to low levels or disappearance of expression in the early postnatal period.\textsuperscript{10–18,30–33} Tissues in which AT2 receptor expression does not substantially regress and disappear in adulthood include brain, uterine myometrium, and adrenal zona glomerulosa and medulla. During fetal life, the AT2 receptor gene is expressed predominantly in areas of active mesenchymal differentiation, but the mRNA expression level decreases rapidly and disappears within days after birth.\textsuperscript{12–15} In the adult, AT2 receptor mRNA has been detected in the adrenal gland, heart, and brain.\textsuperscript{12,33–35} AT2 receptor mRNA is expressed in the fetal and neonatal rat kidney but disappears after the neonatal period and is not expressed in the normal adult.\textsuperscript{12,13} The same also appears to be true for heart.\textsuperscript{8}

Although AT2 receptor mRNA is not expressed in adult kidney, AT2 receptor protein has been detected by immuno-histochemistry and Western blot analysis with the use of a specific polyclonal antibody to the AT2 receptor in the rat kidney.\textsuperscript{17} Consistent with previous reports of AT2 receptor mRNA, receptor protein was mainly observed in the mesenchyme of fetal kidney, and receptor protein expression decreased markedly after birth.\textsuperscript{17} In the newborn kidney, AT2 receptor protein was detected in cortical glomeruli and tubule elements as well as in undifferentiated mesenchymal cells. In adult animals, renal AT2 receptor protein was present predominantly in glomeruli but was markedly diminished compared with that of newborn rats. AT2 receptor protein also was found in small quantities in cortical tubules and interstitial cells in the adult.\textsuperscript{17} The AT2 receptor protein in the adult was upregulated in glomeruli, tubules, and interstitium in response to dietary sodium restriction. The mechanism of reexpression of the AT2 receptor during sodium restriction is unknown. In humans, the AT2 receptor protein is expressed in glomerular, tubular, and vascular elements (Figure 2), but the regulation of receptor protein expression is unknown.

AT2 receptor protein also has been detected in the heart by Western blot analysis and immunocytochemistry.\textsuperscript{18} AT2 receptor protein was present both in myocardium and coronary vessels throughout the ventricle and atrium of neonatal and young adult rat hearts.\textsuperscript{18} AT2 receptor protein was present only in the endothelium and not in smooth muscle cells of coronary arteries.\textsuperscript{18} By Western blot analysis, neonatal rat heart expressed significantly more AT2 receptors than young adult hearts.

Several factors regulate the expression of the AT2 receptor.\textsuperscript{17,36–44} ANG II, norepinephrine, insulin-like growth factor, basic fibroblast growth factor, and transforming growth factor-\textbeta all decrease AT2 receptor expression.\textsuperscript{17,36,37} AT2 receptor expression is increased in experimental heart failure, myocardial infarction, vascular injury, and dietary sodium...
restriction. The reason for the discrepancy between the effects of ANG II and sodium restriction are unclear. Taken altogether, the available evidence suggests that although AT2 receptor mRNA is not expressed in detectable quantities in the adult kidney, heart, and vasculature, the receptor protein is present in a site-specific distribution and may be regulated by physiological maneuvers such as sodium depletion.

General Functions of the AT2 Receptor

The AT2 receptor has several newly described functions related to cell growth, differentiation, and ultimate fate. In general, the AT2 receptor inhibits cell growth and proliferation and promotes cell differentiation, counterbalancing the opposite effects of ANG II at the AT1 receptor. Antiproliferative effects on ANG II by the AT2 receptor have been identified in several different cell types including endothelial cells, neonatal cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells. Recent studies also suggest that the AT2 receptor inhibits angiogenesis. Although there is substantial evidence that the AT2 receptor mediates apoptosis, the findings remain somewhat controversial.

The AT2 receptor has distinctive physiological actions in neuronal cells. AT2 receptors inhibit low-voltage T-type calcium channels in undifferentiated neuronal cells, which express only the AT2 subtype of angiotensin receptors. Biological action is of short duration and therefore it is possible that AT2 receptors could regulate the pacemaker activity of neuronal cells. In neuronal cells from neonatal animals, AT2 receptors activate the delayed rectifier K+ channel leading to increased cellular polarization. In catecholaminergic neurons, the AT2 receptor increases delayed rectifier current and inhibits norepinephrine release initiated by the AT1 receptor. In peripheral neurons, the AT2 receptor increases a neurite-promoting protease, Nexin-1, in Schwann cells. AT2 receptor stimulation also promotes neuronal differentiation, including neurite outgrowth and upregulation of polymerized tubulin. These effects promote neuronal regeneration through the AT2 receptor.

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The AT2 receptor stimulates jejunal sodium and water absorption by a pathway that includes stimulation of the sympathetic nervous system and nitric oxide (NO) production. The final effector of this pathway is cyclic GMP (cGMP), which is released into the interstitial fluid on the serosal side of the transporting epithelial cells. This pathway opposes the actions of ANG II by the AT1 receptor to inhibit sodium and water absorption through a prostaglandin E2-dependent and cAMP-dependent mechanism.

Role of the AT2 Receptor in Renal Function

The renin-angiotensin system plays a major role in the physiological regulation of the kidney, including the control of renal microvascular and tubular function. Before 1996, virtually all studies indicated that the renal actions of ANG II are mediated by the AT1 receptor. As discussed earlier, AT2 receptors are expressed to a low degree in the kidney compared with AT1 receptors. The predominance of renal AT1 over AT2 receptor expression in all likelihood explains past difficulty in eliciting AT2 receptor–related actions. Well-known renal actions of ANG II mediated by the AT1 receptor include increased tubular sodium absorption at low doses, inhibition of reabsorption at higher doses, afferent and efferent arteriolar vasoconstriction, and glomerular mesangial cell contraction and constriction of renal vessels, including the arcuate and interlobular arteries and vasa recta. These actions produce integrated physiological actions including decreased renal blood flow, glomerular filtration rate, and sodium excretion.

In addition to direct effects of ANG II on vascular smooth muscle and tubule cells, the peptide can stimulate the release of vasoactive factors from endothelial, vascular smooth muscle, mesangial, interstitial, or other cell types within the kidney. Thus the vascular and tubular actions of ANG II can be regulated by cell-to-cell (paracrine or autocrine) mediators produced in response to ANG II, thereby dampening or amplifying the primary effects. The most frequent integrated
response to ANG II is net vasoconstriction, and the best known counteracting vasodilator mechanisms include NO and the vasodilator products of arachidonic acid metabolism, especially prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂). ANG II acts directly at vascular smooth muscle cells to increase cytosolic calcium and stimulate phospholipase A₂ (PLA₂), which activates the formation of arachidonic acid. In this manner, it is possible for ANG II to induce renal vasoconstriction. ANG II increases renal NO production, which protects regional and total blood flow.58 Most of the vasodilator action of NO is through cGMP, but NO may exert some of its vasodilator action in the absence of cGMP.59 There is evidence that NO modulates the vasoconstrictor action of ANG II in the afferent but not the efferent arteriole.60 Thus there is convincing evidence that ANG II stimulates NO, which buffers the vasoconstrictor actions of ANG II.

The AT₂ receptor recently has been shown to play an important role in ANG II stimulation of a number of renal vasodilator substances, including bradykinin (BK) and NO. This work was made possible by the introduction of a renal microdialysis technique that could measure small quantities of substances in renal interstitial fluid in vivo in conscious animals.61 In 1996, it was first demonstrated that the AT₂ receptor antagonist PD blocked the increase in cGMP engendered by either dietary sodium restriction or exogenous ANG II administration during normal sodium intake.61 Neither of these responses were affected by the AT₁ receptor antagonist losartan.61 These observations suggested that the renal AT₂ receptor is stimulated to release cGMP in response to the physiological stimulus of sodium depletion. Since these renal responses are not present during normal sodium intake unless exogenous ANG II is given, the major physiological action of ANG II at the renal AT₂ receptor appears to depend on activation of the endogenous renin-angiotensin system. However, the immediate increase in renal cGMP in response to ANG II in sodium-replete animals, which can be blocked completely by PD, strongly suggests that AT₂ receptors are already present in the kidney and do not need to be induced or reexpressed to exert a physiological action.61

AT₂ receptor–induced renal cGMP production is mediated by NO, as both the AT₂ receptor antagonist PD and the NO synthase (NOS) inhibitor L-NNAME blocked the increase in renal cGMP elicited by sodium restriction or exogenous ANG II.62 Since there was no additive inhibition of cGMP when PD and L-NNAME were combined, the increase in renal NO is mediated by the AT₂ receptor. The NOS enzyme(s) responsible for AT₂ receptor stimulation of NO production appear to be multiple, including the neuronal NOS isoform.62

Because BK is also a renal autacoid that stimulates NO production63 through the B₂ receptor,64 it was possible that the AT₂ receptor stimulates a renal BK-NO-cGMP vasodilator cascade. In 1996, it was discovered that the renin-angiotensin system stimulates renal BK production and cGMP formation through the AT₂ receptor.65 Inhibition of renin but not AT₂ receptor blockade decreased markedly the elevated renal BK levels measured during sodium depletion.65 This study initiated the concept that the AT₂ receptor releases BK and NO. In 1999, the ability of ANG II to stimulate BK production was confirmed.66 Exogenous ANG II increased renal BK in conscious rats, and this response was abrogated completely by PD but was not influenced by losartan.66 Neither PD nor losartan affected BK in the absence of exogenous ANG II, which suggests that activation of the renin-angiotensin system is once again required.66

The evidence cited above formed the basis for a vasodilator/natriuretic cascade (Figure 3) wherein ANG II activates the AT₂ receptor, resulting in the increased production of BK and NO. Alternatively, AT₂ receptor stimulation could increase BK, which alone could be responsible for increasing NO and cGMP. These results have been confirmed by studies in stroke-prone spontaneously hypertensive rats, in which AT₂ receptor stimulation increased aortic cGMP by increasing BK and NO formation.67

Studies in genetically engineered mice lacking the AT₂ receptor (AT₂-Null) have now confirmed the concept that the AT₂ receptor mediates a BK-NO-cGMP vasodilator cascade.68 These animals are essentially normotensive under basal conditions69,70 but have profound and sustained pressor and antidiuretic/antinatriuretic hypersensitivity to ANG II. AT₂-Null mice were found to have very low basal renal levels of BK and cGMP.68 In response to dietary sodium restriction or exogenous ANG II for 1 week, AT₂-Null failed to increase either BK or cGMP, which increased severalfold in wild-type mice (WT). Taken altogether, the evidence confirms the concept that the AT₂ receptor physiologically mediates the renal production of BK and NO. These studies further suggest that the absence of the AT₂ receptor and its vasodilator/natriuretic cascade is responsible for the markedly increased sensitivity of blood pressure and sodium excretion to ANG II in AT₂-Null mice.

In addition to the above-mentioned mechanisms, there is evidence that an AT₂ receptor located in the apical membrane of renal proximal tubule cells is linked to PLA₂, whereby arachidonic acid is released and metabolized by cytochrome P450 epoxygenase.71 Recent in vitro studies demonstrate that the proximal tubule AT₂ receptor is linked to inhibition of sodium and bicarbonate absorption, an effect that opposes AT₁ receptor–mediated absorption.72 These studies are quite consistent with the demonstrated natriuretic role of AT₂ receptors in vivo.68
Several studies have suggested a role for AT₂ receptors in renal eicosanoid production and metabolism. The major renal vasodilator prostanoid is prostaglandin E₂ (PGE₂) and its formation occurs in response to ANG II as a result of PLA₂ release of substrate arachidonic acid.⁷³ PGE₂ is formed within the kidney as a result of ANG II stimulation of the AT₁ receptor.⁶¹ The possibility that the AT₂ receptor might be involved in renal prostaglandin metabolism was introduced when it was shown that AT₂ receptor blockade in rats on a low sodium diet increased renal PGE₂.⁶¹ This increase in PGE₂ could be related to an effect of the AT₂ receptor on PGE₂ metabolism. Prostaglandin F₂α (PGF₂α) can be formed directly from PGE₂ by PGE₂ 9-ketoreductase or directly from the precursor prostanoid, PGH₂. It was found that the AT₂ receptor increases PGF₂α formation, probably by stimulating conversion from PGE₂, since the ratio of PGF₂α to PGE₂, a measure of such conversion, is markedly decreased with AT₂ receptor blockade.⁷⁴ This interpretation is consistent with the demonstrated upregulation of PGE₂ 9-ketoreductase by sodium depletion.⁷⁵ Nonetheless, it remains possible that the AT₂ receptor selectively limits the production of PGF₂α but not PGE₂ from PGH₂.

In accord with the above observations, AT₂-Null mice have increased renal PGE₂ and PGI₂ and decreased PGF₂ both basally and in response to sodium depletion or exogenous ANG II.⁷⁶ The renal vasodilator prostanoids, PGE₂ and PGI₂, were both stimulated by AT₁ receptors, providing counter-regulatory vasodilation in opposition to the AT₁ receptor–mediated vasoconstrictor action of ANG II. In addition, very high renal cAMP levels in AT₂-Null compared with WT were normalized by blockade of the AT₁ receptor, which reduced PGE₂ and PGI₂ to low levels.⁷⁶ This raises the likelihood that these vasodilator prostanoids act physiologically through stimulation of adenylyl cyclase and cAMP production. Figure 3 summarizes the effects of AT₁ and AT₂ receptors on renal prostaglandin production and metabolism.

There also is evidence that the AT₂ receptor mediates vasodilation in the rabbit afferent arteriole through a cytochrome P-450 pathway, possibly by means of epoxyeicosatrienoic acid.⁷⁷ Activation of the AT₂ receptor modulates AT₁ receptor–mediated vasoconstriction in the afferent arteriole of the spontaneously hypertensive rat.⁷⁸ The vasodilator action of ANG II stimulation of the AT₂ receptor in these direct vascular studies confirms the results of the studies in vivo.

The net effect of ANG II on renal function is a combination of AT₁ and AT₂ receptor–mediated events with the AT₁ receptor–mediated effects generally predominant. Thus ANG II administration results in net renal vasoconstriction and reduced glomerular filtration. These effects are modulated, however, by AT₂ receptor–stimulated BK, NO, and cGMP. The net sodium excretory response to ANG II depends on its concentration: Low concentrations inhibit sodium excretion, whereas higher concentrations induce natriuresis. At this time, we are still unsure which receptor mediates the natriuretic response to high concentrations of ANG II.

Role of the AT₂ Receptor in Control of Blood Pressure

As discussed earlier, AT₂-Null mice have slightly elevated blood pressures compared with WT, but still well within the normotensive range.⁶₈–⁷₀,⁷₄ Stimulation with exogenous ANG II, either acutely or chronically, increases blood pressure to a much greater extent in AT₂-Null than WT. AT₂-Null infused with a low dose of ANG II (4 pmol/kg per minute) that does not affect blood pressure in WT increases blood pressure substantially into the hypertensive range in AT₂-Null.⁶₈ This increase in blood pressure response to ANG II in the absence of the AT₁ receptor is accompanied by deficiency of the BK-NO-cGMP vasodilator cascade, the absence of which causes the ANG II hypersensitivity. A possible additional reason for the ANG II hypersensitivity may be upregulation of AT₁ receptors triggered by AT₂ receptor deficiency.⁷⁹,⁸₀ However, AT₁ receptor upregulation would not account for the deficiency of vasodilator autacoids in this model.

The elevation of PGE₂ and PGI₂ in AT₂-Null suggested the possibility that these vasodilator prostanoids might prevent hypertension in this model. Reduction of PGE₂ and PGI₂ with indomethacin, a cyclooxygenase inhibitor, resulted in a progressive and sustained increase in blood pressure well into the hypertensive range in AT₂-Null while having no effect on blood pressure in WT.⁷⁶ Therefore, in AT₂-Null, increased vasodilator prostanoids prevent hypertension that otherwise would accompany the hypersensitivity of blood pressure and sodium excretion to ANG II. This is an unusual example of the vasodilatory capacity of prostanoids in physiology.

The BK-NO-cGMP vasodilator cascade mediated by the AT₂ receptor suggested the possibility that the AT₂ receptor may subserve a protective role in blood pressure regulation. In a 2-kidney, 1-wrap model of renal vascular hypertension, activation of the renin-angiotensin system increases blood pressure through the AT₁ receptor. Blood pressure reduction with AT₁ receptor blockade with losartan was prevented by AT₂ receptor blockade with PD and by use of the BK-B₂ receptor antagonist icatibant.⁶⁶ Similar data are available for 2-kidney, 1-clip Goldblatt hypertensive animals (Carey, unpublished observations). Thus the AT₂ receptor engenders counterregulatory vasodilatation and protects against a further increase in blood pressure in these models of angiotensin-dependent hypertension. Abrogation of the hypotensive action of AT₁ receptor blockade with AT₂ receptor inhibition suggests that at least some of the beneficial effects of AT₁ receptor blockade are mediated by the AT₂ receptor, possibly by the BK-NO-cGMP vasodilator cascade.

In the 2-kidney, 1-wrap model of angiotensin-dependent hypertension, the vasodilator autacoids BK, NO, and cGMP were markedly decreased in the ischemic kidney and augmented in the contralateral kidney.⁶⁶ The increase in vasodilator autacoids in the contralateral kidney was due to AT₂ receptor stimulation, since these were inhibited to control levels with PD.⁶⁶ In the ischemic kidney, the AT₃a receptor protein was downregulated in both kidneys, whereas the AT₂ receptor was downregulated only in the ischemic kidney.⁴⁴ Therefore the protective effect of the AT₂ receptor is probably mediated by augmentation of a BK-NO-cGMP vasodilator.
The role of AT₁ and AT₂ receptors in blood pressure regulation.

In parallel with studies of angiotensin-dependent hypertension, investigators have demonstrated a role for the AT₂ receptor in the regulation of blood pressure in normal salt-restricted rats. In salt-restricted rats, AT₂ receptor blockade with PD was found to offset the blood pressure–lowering effect of losartan or valsartan, which suggests that AT₁ receptor blockade lowers blood pressure, at least in part, by stimulation of AT₂ receptors caused by increased ANG II.

The discovery that the AT₂ receptor mediates a BK-NO-cGMP vasodilator cascade has recently been confirmed in mice overexpressing the AT₂ receptor selectively in vascular smooth muscle cells. In this study, AT₂ receptor expression was increased from low levels (7.5%) to ≈ 39% of the expression of the AT₁ receptor. Animals with AT₂ receptor overexpression were normotensive. However, pressor responses in vivo and vasoconstriction in vitro to ANG II were absent in animals overexpressing the AT₂ receptor. In animals overexpressing the AT₂ receptor, vasoconstrictor responses to ANG II were restored with AT₂ receptor blockade and also with BK-B₂ receptor blockade or with NOS inhibition. The initiating event was proposed as AT₂ receptor activation of kininogenase through cellular acidification to induce BK production, but the early part of the pathway is still controversial. Several studies from Sassard’s group have indicated that pressure-natriuresis is inhibited by the AT₂ receptor. The majority of reports, however, indicate that the AT₂ receptor stimulates pressure-natriuresis. In rats with 2-kidney, 1-wrap renovascular hypertension, pressure-natriuresis in the nonischemic kidney is accompanied by maintenance of AT₂ receptor expression and an increase in AT₂ receptor–dependent BK, NO, and cGMP. In AT₂-Null mice, an increase in pressure with ANG II is accompanied by a sustained antinatriuresis. Also, AT₂-Null mice have their pressure-natriuresis curves shifted rightward in association with reduced renal cortical and medullary blood flow. Resolution of these differences is important because virtually all hypertensive processes are accompanied by a reduction in pressure-natriuresis resulting in renal sodium retention. Figure 4 summarizes the role of AT₁ and AT₂ receptors in blood pressure regulation.

Opposing Actions of AT₁ and AT₂ Receptors

As is true for other peptide receptor families, the interaction between receptor subtypes within a family may be important to the physiological response to the agonist. In general, ANG II effects at the AT₁ receptor are opposed by actions at the AT₂ receptor. This principle applies to neuronal effects, actions on cell proliferation and differentiation, angiogenesis, and chronotropic effects in the heart. As is true for other peptide receptor families, the interaction between receptor subtypes within a family may be important to the physiological response to the agonist. In general, ANG II binding to AT₁ receptors increases inositol phosphate production, whereas ANG II inhibits inositol phosphate production by the AT₂ receptor. In the gastrointestinal tract, AT₁ receptors oppose AT₂ receptors in sodium and water absorption, and there is clear physiological opposition between these receptors as sodium transport is finely tuned.

In the kidney, the AT₁ receptor induces vasoconstriction and sodium retention, whereas the AT₂ receptor promotes vasodilation and natriuresis. AT₂ receptor blockade prevents the hypotensive effects of AT₁ receptor blockade and the AT₂ receptor mediates the depressor response to ANG II.

In general, the AT₁ receptor stimulates protein phosphorylation and the AT₂ receptor stimulates protein dephosphorylation, which counterbalances the effects of protein kinases, especially MAP kinase, stimulated by the AT₁ receptor. Figure 5 indicates the role of AT₂ receptors in counterbalancing the actions of AT₁ receptors.

Physiologic Role of the AT₂ Receptor

The AT₂ Receptor Counterbalances the Effects of the AT₁ Receptor

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Figure 5. Schematic depiction of the balance of actions mediated by AT₁ and AT₂ receptors. AT₁ receptor actions are shown on the left and counterbalancing actions of AT₂ receptors on the right.
Conclusions

The past 5 years have witnessed a dramatic change in the way we view the renin-angiotensin system. Until recently, the vascular and renal actions of ANG II were thought to be transduced solely through the AT₁ receptor, and the function of the AT₂ receptor was unknown. However, recent information has emerged in support of a role for the AT₂ receptor in the regulation of blood pressure and kidney function. The AT₂ receptor mediates a vasoconstrictor/antinatriuretic pathway of ANG through the AT₁ receptor and plays a protective role in renal vascular hypertension. The AT₂ receptor also modulates renal prostaglandins, which play an important role in blood pressure regulation. Further studies in AT₁ and AT₂ receptor-deficient animals will help clarify these mechanisms. From the actions described for the AT₂ receptor thus far, one would logically predict that a specific AT₂ receptor agonist may have beneficial and protective advantages in the treatment of hypertension and renal and cardiovascular disease.

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