Physiological and Pathophysiologica l Functions of the AT\textsubscript{2} Subtype Receptor of Angiotensin II
From Large Arteries to the Microcirculation
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Abstract—Angiotensin II exerts a potent role in the control of hemodynamic and renal homeostasis. Angiotensin II is also a local and biologically active mediator involved in both endothelial and smooth muscle cell function acting on 2 receptor subtypes: type 1 (AT\textsubscript{1}R) and type 2 (AT\textsubscript{2}R). Whereas the key role of AT\textsubscript{1}R in the development of the embryo has been extensively studied, the role of AT\textsubscript{2}R in the adult remains more questionable, especially in humans. In vitro studies in cultured cells and in isolated segments of aorta have shown that AT\textsubscript{2}R stimulation could lead to the production of vasoactive substances, among which NO is certainly the most cited, suggesting that acute AT\textsubscript{2}R stimulation will produce vasodilation. However, in different organs or in small arteries isolated from different type of tissues, other vasoactive substances may also mediate AT\textsubscript{2}R-dependent dilation. Sometimes, such as in large renal arteries, AT\textsubscript{2}R stimulation may lead to vasoconstriction, although it is not always seen. In isolated arteries submitted to physiological conditions of pressure and flow, AT\textsubscript{1}R stimulation may also have a role in shear stress–induced dilation through an endothelial production of NO. Thus, when acutely stimulated, the most probable response expected from AT\textsubscript{2}R stimulation will be a vasodilation. Therefore, in the perspective of a chronic AT\textsubscript{1}R blockade in patients, overstimulation of AT\textsubscript{2}R might be beneficial, given their potential vasodilator effect.

Concerning the possible role of AT\textsubscript{2}R in cardiovascular remodeling, the situation is more controversial. In vitro AT\textsubscript{1}R stimulation clearly inhibits cardiac and vascular smooth muscle growth and proliferation, stimulates apoptosis, and promotes extra cellular matrix synthesis. In vivo, the situation might be less beneficial if not deleterious; indeed, if chronic AT\textsubscript{2}R overstimulation would lead to cardiovascular hypertrophy and fibrosis, then the long-term consequences of chronic AT\textsubscript{2}R blockade, and thus AT\textsubscript{2}R overstimulation, require more in-depth analysis. (Hypertension. 2001;38:1150-1157.)

Key Words: blood pressure ■ growth ■ hypertrophy ■ vascular ■ endothelium ■ relaxation

Disorders of the renin-angiotensin system contribute largely to the pathophysiology of hypertension, renal diseases, and congestive heart failure. Angiotensin (Ang) II exerts hemodynamic and renal effects, but it is also a local biologically active mediator with direct effects on endothelial and smooth muscle cells.\textsuperscript{1} Two major subtypes of Ang II receptors, type 1 (AT\textsubscript{1}R) and type 2 (AT\textsubscript{2}R), have been identified; their roles have now been investigated in more depth in vivo and in vitro, although few data are available concerning the role of these receptors, especially AT\textsubscript{2}Rs, in the adult circulation in humans. These 2 subtypes, first distinguished on a pharmacological basis, have been identified by expression cloning from various species, including humans. They both share a seven-transmembrane domain topology. However, they display striking differences in many aspects.

The AT\textsubscript{2}R subtype is expressed ubiquitously and is involved in all the well-known biological functions of Ang II, although it is mostly studied at concentrations that are extraordinarily high compared with physiological concentrations (\textmu molar versus picomoles). The intracellular signal transduction events triggered by AT\textsubscript{2}R (with Ang II in the \textmu molar range) are well characterized and include G protein coupling, as well as activation of several tyrosine kinases.

In contrast to AT\textsubscript{1}Rs, the physiological role of AT\textsubscript{2}Rs has long remained an enigma.\textsuperscript{1} It is highly expressed in fetal tissues, although its expression is dramatically decreased after birth, being restricted to a few organs, including the cardiovascular system. The AT\textsubscript{2}R is re-expressed in the adult animal after cardiac and vascular injury and during wound healing, suggesting a role for this receptor in tissue remodeling.
growth, and/or development. A major step toward the understanding of AT_{2} R functions has recently been provided by the generation of genetically engineered animals either lacking or overexpressing the gene encoding for the AT_{2} R.

The role of the AT_{2} R is important to determine as it may possibly be involved in hypertensive patients receiving a chronic treatment of AT_{1} R antagonists. Besides their effect on blood pressure, long-term administration of AT_{2} R blockers results in a several-fold increase in plasma Ang II and thus in a possible overstimulation of AT_{2} Rs. Therefore, the effect of the stimulation of the AT_{2} R is becoming increasingly important in both physiological and pathological situations. Furthermore, a cross-talk between the 2 receptor subtypes (AT_{1} R and AT_{2} R) has been described, and AT_{2} R blockade might also unmask potential effects of AT_{2} Rs that were inhibited by AT_{1} R stimulation.

In the present review, we focused on the cardiovascular role of the Ang II AT_{2} R subtype in adult animals and humans and thus excluded its role during growth and development. We report the possible roles of the AT_{2} R in the control of the vasomotor tone and the more speculative role of the AT_{2} R in the Ang II–induced cardiovascular remodeling.

**Location of AT_{2} R in the Adult**

The AT_{2} R gene expression is high during fetal life and decreases rapidly after birth. In adults, the AT_{2} R seems restricted to some vascular territories, and this location may change in situations such as pregnancy or in pathological situations such as hypertension, heart failure, or vascular injury (see review articles).

In animals, AT_{2} Rs were found in many vessel types. Briefly, AT_{2} Rs are present in the uterus, the kidney, the portal circulation, the heart, and the brain. Whereas the aorta has been the most commonly used model in the investigation of AT_{2} R functions

(see below), in small resistance arteries AT_{2} Rs are also present in the endothelial and/or smooth muscle cells, depending on the vessel type and species. Using immunofluorescence, AT_{2} Rs were localized in endothelial and smooth muscle cells in rat mesenteric arteries and skeletal muscle arterioles, (Figure 1).

In humans, the presence of AT_{2} Rs in the adult vasculature remains to be further demonstrated, as only scarce information is available. Although no AT_{2} R was detected in vascular smooth muscle cells from renal arteries using the radio-labeled AT_{2} R ligand CGP-42112, in the human kidney AT_{2} R expression was localized using in situ hybridization to the medial layer of the interlobular arteries. In human kidney arterioles, AT_{2} Rs are mainly located to the adventitia and only detected with a low level in the endothelium. In coronary vessels, AT_{2} Rs were detected and remained unchanged or upregulated in the failing heart. In primary cell cultures, AT_{2} R transcripts are found in coronary endothelial cells and in human umbilical vein endothelial cells (HUVECs). Human uterine arteries also express a large number of AT_{2} Rs. Thus, although the AT_{2} R is present in the adult vasculature, its distribution is not homogeneous and is subject to changes according to age, species, vessel type, and pathological state.

**Role of AT_{2} R in the Control of Vascular Tone and Arterial Pressure**

A role for the AT_{2} R in the control of vascular tone can be deduced from both in vivo and in vitro experiments. During the past decade, the role of the acute stimulation of the AT_{2} R has been investigated in several vascular territories and especially in the kidney, uterus, and mesentery. These studies have been performed in isolated arteries, in vitro, or in perfused organs (hindlimb, mesenteric bed, or kidney); the experimental conditions were quite often different, making it difficult to have a clear view on the exact role of the AT_{2} R. Finally, most of these studies have been performed in animals, and the effect of acute stimulation of AT_{2} R remains to be determined in humans.

**Experimental Evidence Obtained In Vivo or In Situ**

In anesthetized rats, a bolus injection of Ang II induces a biphasic response with an initial rise in blood pressure due to AT_{1} R activation and a latter slow decrease in pressure that has been attributed to AT_{2} Rs. In rats submitted to a high-salt diet, Ang II infusion produces a higher rise in blood pressure when co-infused with the AT_{2} R blocker PD 123,319, suggesting that AT_{2} Rs have a vasodilator effect in these experimental conditions. However, in similar Ang II perfusion conditions, Macari et al reported that PD 123,319 did not affect blood pressure, whereas high doses of CGP-42112, an AT_{2} R agonist, increased blood pressure, suggesting that CGP-42112 behaves as a nonspecific AT_{2} R agonist when used at a high concentration.

Experimental protocols involving local injections of Ang II allow appreciation of the diversity of the involvement of AT_{2} R in the control of vasomotor tone in different regional networks. Intra-mesenteric injection of Ang II induces a rise in pressure, sensitive or insensitive to AT_{2} R blockade,
AT-R does not seem involved in Ang II–induced increase in vascular resistance in the isolated rat heart and in the rat hindquarter. In the control of cerebral blood flow, as assessed by measurements performed using laser Doppler flow probes in anesthetized rats, the AT-R does not seem to play a major role in baseline conditions. Similarly, AT-R blockade has no effect on the decrease in cerebral blood flow caused by Ang II when injected into the carotid artery. In contrast, in the in situ perfused kidney, AT-R blockade decreases Ang II–dependent vasoconstriction when NO synthesis is inhibited. From these in vivo or in situ perfused organs experiments, it can be deduced that AT-Rs play a weak role in the control of systemic blood pressure under normal physiological conditions. However, the AT-R likely plays a role in the local control of blood flow in several organs. The great diversity of the possible responses to AT-R stimulation, depending on the location, may explain the near absence of in vivo effect of AT-R blockade, although in some situations AT-R activity might be revealed after AT-R blockade (possible cross-talk between AT-R and AT-R) or NO synthesis inhibition (see below).

A role for AT-R in the control of blood pressure can also be deduced from the studies in AT-R knockout mice that have high blood pressure. These mice also exhibit a higher increase in blood pressure and a higher increase in total peripheral vascular resistance following a low-dose infusion of Ang II. In mice overexpressing AT-R in vascular smooth muscle lose their ability to raise blood pressure after Ang II infusion, whereas they become responsive to Ang II after NO synthesis blockade or AT-R blockade. Therefore, data from transgenic mice for the AT-R suggest that the AT-R plays a vasodilator role, lowering blood pressure. Thus, according to these results, selective stimulation of AT-R in the presence of AT-R antagonists is predicted to have a beneficial clinical effect in controlling blood pressure. Recently, this effect has been demonstrated in SHR.

Role of AT-R in the Control of Vasomotor Tone and Blood Flow In Vitro

In Renal Circulation

In the renal circulation, AT-R stimulation seems to have a vasodilator effect in mid-size and large arterioles in the rat as AT-R blockade with PD 123,319 reduces Ang II–induced contraction of intralobular renal arteries in the perfused hydronephrotic kidney. Nevertheless, PD 123,319 failed to affect Ang II–dependent vasconstriction in isolated rabbit renal arteries. Dual effect of AT-R stimulation on large and small arteries has been reported: on larger arterioles AT-R stimulation might result in vasodilation, whereas on small arterioles AT-R activation produces vasoconstriction. Indeed, in isolated and perfused afferent arterioles, AT-R stimulation mediates an endothelium-dependent dilation sensitive to cytochrome P 450 (CyP450) blockade. The mediators involved might be epoxy-eicosatrienoic acids. This vasodilatory effect of AT-R may antagonize AT-R–dependent contraction in these arterioles in normotensive but not young hypertensive (SHR) rats. This defect in AT-R–dependent dilation in arterioles from young SHR might play a role in the pathogenesis of hypertension. Finally, in mice lacking the gene for AT-R, ACE activity is doubled in the kidney, suggesting that AT-R stimulation might downregulate the activity of the enzyme.

In the Uterus

In the uterus, AT-R are widely expressed in the myometrium. In the uterine artery, AT-R are also expressed in ewes and rats and their number increases tremendously during pregnancy. In rat ureter arteries, isolated in a small vessels myograph, Ang II–induced contraction is attenuated by AT-R stimulation with CGP-42112 and is increased after AT-R blockade with PD 123,319, whereas phenylephrine-induced tone is unaffected. This effect of AT-R is less pronounced during pregnancy, which fits with a downregulation of myometrial AT-R.

In the Cerebral Circulation

In the cerebral circulation, Ang II has been shown to dilate arteries when applied topically on a cranial window in anesthetized rats. This relaxation is mediated by cyclooxygenase derivatives (the relaxation was sensitive to indomethacin) produced by the endothelium. On the other hand, in isolated rat, bovine, or canine cerebral arteries (≥150 to 200 μm ID), Ang II induces a contraction. The role of AT-R in this contraction is not yet understood. Nevertheless, in vivo measurements (detailed above in Experimental Evidence Obtained In Vivo or In Situ) failed to show a role for AT-Rs in cerebral blood flow. This might reflect the heterogeneity of the responses to AT-R stimulation in cerebral vessels from different size and location.

In the Mesenteric Circulation

In perfused and pressurized isolated mesenteric resistance arteries, Ang II–induced contraction is independent of AT-R in adult normotensive rats and SHR, but in young prehypertensive SHR Ang II–induced contraction involves both AT-R and AT-R. This double involvement of AT-R and AT-R in Ang II–induced contraction was not found in age-matched young normotensive rats. Thus, in young SHR, the involvement of the 2 types of receptor might explain the hyperreactivity of the arteries in SHR and contribute to the development of hypertension. In mesenteric isolated vessels, AT-R are also involved in the Ang IV–dependent dilation.

In mesenteric arteries, AT-Rs also have a role in the control of the vascular tone by flow (shear stress). In resistance arteries, pressure induces an active vasoconstrictor (myogenic) tone that is opposed by flow-induced dilation. Flow (shear stress)-induced dilation depends mainly on the release of endothelium-derived relaxing factors, and the local tissue renin-angiotensin has the ability to interact with flow-induced dilation. Although locally produced Ang II is a potent amplifier of vascular tone, Ang II is also able to interact with flow-dependent dilation. AT-R blockade (PD 123,319) reduces the amplitude of flow (shear stress)-induced dilation in rat mesenteric arteries. Blockade of AT-R had no effect on arterial diameter changes due to flow, but the nonselective inhibitor sarafaslin (blocking both AT-R and AT-R) produced an effect similar to that of PD 123,319, confirming the role AT-R in flow-dependent dilation. This
mediated contraction and AT\textsubscript{2} R-mediated dilation below). It is also important to note that a cross-talk between AT\textsubscript{1} R and AT\textsubscript{2} R function by AT\textsubscript{1} R. Contractions induced by another agonist U46619 were not affected by AT\textsubscript{2} R blockade, although in young SHR AT\textsubscript{2} R may also contribute to Ang II–induced contraction in hypertensive rats are not known.\textsuperscript{13} In the kidney, AT\textsubscript{2} R-dependent contraction is proposed to involve CyP450 metabolites such as 20-HETE.\textsuperscript{34,64}

**Mediators Involved in the Acute Vascular Response to AT\textsubscript{2} R Stimulation**

**Mediators Involved in the AT\textsubscript{2} R-Mediated Contraction**

In mesenteric arteries, the mediators involved in AT\textsubscript{2} R-dependent contraction in hypertensive rats are not known. In the kidney, AT\textsubscript{2} R-dependent contraction is proposed to involve CyP450 metabolites such as 20-HETE.\textsuperscript{34,64}

**Mediators Involved in the AT\textsubscript{2} R-Mediated Dilation**

Although the aorta is not, per se, involved in the local control of blood flow, it is the most commonly used experimental model in the study of receptor function. Ang II increases cGMP content in the aorta from rabbits and rats. In the rat aorta, this increase in cGMP content is exclusively dependent on the AT\textsubscript{1} R,\textsuperscript{59} although both AT\textsubscript{1} R and AT\textsubscript{2} R are expressed in the rabbit aorta.\textsuperscript{65} In rings of the rat aorta, the inhibitory affect of AT\textsubscript{2} R on phenylephrine-induced contraction depends on the production of NO.\textsuperscript{3} Ang II–induced cGMP production depends on AT\textsubscript{2} R in SHR and in stroke-prone hypertensive rats, in which AT\textsubscript{2} R stimulation increases NO synthesis and cGMP production through the activation of the bradykinin B\textsubscript{2} receptor.\textsuperscript{66} In SHR, the inhibition of Ang II–induced contraction by losartan is attenuated by AT\textsubscript{1} R blockade.\textsuperscript{3} This latter study also suggests a downregulation of AT\textsubscript{2} R function by AT\textsubscript{2} R.\textsuperscript{3} Contractions induced by another vasoconstrictor such as the thromboxane A\textsubscript{2}/PGH\textsubscript{2} receptor agonist U46619 were not affected by AT\textsubscript{2} R blockade, although they were sensitive to AT\textsubscript{1} R blockade.\textsuperscript{67} Finally, AT\textsubscript{2} R knockout in mice induces a decrease in aortic cGMP content, together with an overexpression of the AT\textsubscript{1} R.\textsuperscript{68} On the contrary, AT\textsubscript{2} R transgenic mice overexpressing the AT\textsubscript{2} R have a high aortic cGMP content normalized by either NO-synthesis blockade or bradykinin B\textsubscript{2} receptor blockade.\textsuperscript{38} This AT\textsubscript{2} R-dependent bradykinin production might be mediated by an intracellular acidosis, which would activate an acid-optimum kininogenase.\textsuperscript{38}

A clear relation between AT\textsubscript{1} R-stimulation and the NO-cGMP pathway has been shown in several conditions and in different types of arteries. In mesenteric resistance arteries, AT\textsubscript{1} R-dependent flow-mediated dilation is lost after NO-synthesis blockade or endothelium disruption.\textsuperscript{14} Thus, AT\textsubscript{2} Rs located on endothelial cells could trigger a release of NO after shear stress stimulation in these vessels.

In coronary microvessels, NO production depends on both AT\textsubscript{1} R and AT\textsubscript{2} R.\textsuperscript{61} The involvement of bradykinin as a
mediator between AT_1R stimulation and NO production is supported by experiments performed in transgenic mice overexpressing the AT_2R and also in stroke-prone SHR. In these rats, a 4-hour infusion of Ang II increases the aortic cGMP content. This effect was inhibited by either AT_1R blockade, NO-synthesis inhibition, or bradykinin B_2 receptor blockade.66 The relation between AT_1R, bradykinin, and NO has been evidenced in vascular smooth muscle cells but remains to be explored in endothelial cells.

Other mechanisms may be involved in AT_2R-mediated dilation. In isolated afferent arterioles from the rabbit kidney, AT_2R blockade with PD 123,319 suppresses the facilitatory effect of miconazole on Ang II–induced contraction without affecting the effect of nitro-L-arginine methyl ester, suggesting that in this vessel the AT_2R mediates a dilation, probably through the release of epoxy-eicosatrienoic acids.11 In quiescent HUVECs, AT_2R blockade increases Ang II–induced superoxide formation,23 which could reduce the Ang II–induced contraction in blood vessels. The AT_2R-dependent inhibition of AT_2R-mediated superoxide formation involves tyrosine phosphatases.23 Indeed, AT_2Rs have previously been shown to activate phosphotyrosine phosphate activity in different cell types.7,69–71 Similarly, Ang II–dependent contraction might be reduced in situ thanks to a possible inhibitory effect of the AT_2R on ACE activity in different organs. Indeed, in AT_2R knockout mice, circulating and tissue (heart, lung, and kidney) ACE activity is doubled.43 This increased ACE in AT_2R knockout mice leads to a higher vasoconstrictor effect of Ang I and to a lower vasodilatory effect of bradykinin.43 This AT_2R-dependent inhibition of ACE activity was also observed, by the same authors, in wild-type mice after an acute inhibition of the AT_2R with PD 123,319.43

Regulation of AT_2R
As described above, as a possible mechanism for the vasodilatory effect of AT_2R stimulation, the AT_2R-mediated attenuation of AT_1R-dependent contraction is a way by which AT_2Rs can downregulate AT_1R-dependent function. On the other hand, a downregulation of AT_2Rs by AT_1Rs has also been reported. In aortic rings from SHR, AT_1R blockade with losartan reduces phenylephrine-induced contraction; this reduction is inhibited by either NO-synthesis blockade (nitro-L-arginine methyl ester) or AT_2R blockade with PD 132,319.3 Furthermore, the AT_2R-dependent NO production can only be observed after AT_1R blockade, suggesting an inhibitory effect of AT_2Rs on AT_1Rs. AT_2Rs may also be regulated by other endocrine systems, as insulin increases the expression of AT_2Rs in rat aortic smooth muscle cells72 and adrenocorticotropic hormone decreases the density of AT_2Rs in the uterine arteries of ewes.9

Effect of AT_3Rs in the Control of Cardiovascular Structure
Recent clinical trials of ACE inhibitors have consistently documented the salutary effects of this class of agents in treating and preventing cardiovascular disease, with impressive reductions in coronary and cerebral vascular events despite a modest effect on blood pressure lowering.73–75 These data suggest that ACE inhibitors may also exert direct actions on blood vessels beyond their hemodynamic effects. ACE inhibitors have also demonstrated marked effects on the cardiovascular remodeling associated with hypertension, mainly hypertrophy and fibrosis. Therefore, the effect of Ang II and its receptor subtypes on vascular remodeling deserves to be examined. In vitro, Ang II triggers vascular smooth muscle cell hypertrophy and/or hyperplasia,76,77 this effect being mediated by the AT_1R. In organ culture of isolated segments of rabbit aorta maintained under physiological pressure and flow, Bardy et al78,79 have reported that mechanical factors stimulated a local synthesis of Ang II, which in turn induces an increase in the synthesis of extracellular matrix proteins, such as fibronectin and collagen, via the AT_2R. In the same way, van Kleef et al80 reported that AT_2Rs, but not AT_1Rs, mediate the progression of neointimal thickening induced by delayed application of Ang II in the injured carotid artery in the rat.81 Mifune and coworkers82,83 aimed to examine the effects of stimulation of AT_2Rs on collagen synthesis in vascular smooth muscle cells. Because in vitro cultured vascular smooth muscle loses the AT_2R subtype, retroviral gene transfer was used to supplement adult vascular smooth muscle cells with AT_2Rs to mimic the vasculature in vivo. The treatment of these cells with the AT_2R agonist CGP-42121A alone did not cause a significant change in p42/p44 mitogen-activated protein kinase activity but caused a 30% to 50% decrease in protein tyrosine phosphatase activity. Treatment with CGP-42112A also caused a dose- and time-dependent increase in collagen synthesis, which was completely inhibited by the AT_2 antagonist PD 132,319, unaffected by the AT_1 antagonist losartan, and attenuated by a treatment with pertussis toxin or G_i antisense oligonucleotides. Interestingly, studies in other cell lines demonstrated that CGP-42112A caused similar results in transfected mesangial cells but had essentially opposite effects in fibroblasts (NIH-3T3-AT2). These results suggest that AT_2R stimulation can increase collagen synthesis in vascular smooth muscle cells via a G_i-mediated mechanism and provide evidence for heterogeneity in the effects of AT_2R stimulation in different tissues.82

The effect of the AT_1R on extracellular matrix synthesis in cardiac tissues was studied in cardiomyopathic hamsters.83 AT_1R density increases by 153% during heart failure, whereas AT_2R density increases in the hypertrophy stage and then returns to control level during heart failure. Such differential regulation of AT_2Rs and AT_1Rs during heart failure is consistent with changes in the respective mRNA levels.83 Cardiac fibroblasts isolated from cardiomyopathic hearts from hamsters during heart failure, but not from controls, expressed AT_2R. Using the cardiac fibroblasts expressing AT_1Rs, Ohkubo et al84 found that Ang II stimulates net collagen protein production. Pretreatment with an AT_2R antagonist (PD 132,319) evokes a further elevation in collagen and fibronectin synthesis.

In vivo, Ang II is involved in the increase in cardiovascular fibrosis, which is a pathological feature associated with hypertension.84–86 In the myocardium, the progressive interstitial and perivascular fibrosis contribute to increase the stiffness of the cardiac muscle and to develop diastolic
dysfunction. Indeed, Ang II is involved in the development of cardiomyocyte hypertrophy and cardiac fibrosis and in the modulation of cardiac fibroblast growth and collagen synthesis in human and animal models.\textsuperscript{67,68} Clearly, 1 major role of the \textit{AT}_2R lies in developmental processes as well as in vascular cardiac remodeling. Most of the reports indicate antiproliferative, antiapoptotic, and antifibrotic effects of the \textit{AT}_2R in the fetus and in damaged tissues. Being first reported to inhibit neointima formation after vascular injury, \textit{AT}_2R has more recently been shown to contribute to growth inhibition in fetal vascular smooth muscle cells and in hypertrophied hearts.\textsuperscript{89} \textit{AT}_2R stimulation was also reported to reduce interstitial fibrosis in failing cardiomyopathic hearts.\textsuperscript{83}

However, several recent reports of in vivo and in vitro studies using receptor subtype specific blockers and antisense DNA suggest a possible role of the \textit{AT}_2R in medial hypertrophy and fibrosis in the aorta and cultured cells. In rats receiving hypertensive doses of Ang II, chronic blockade of the \textit{AT}_2R did not affect the plasma level of Ang II and the vascular reactivity to Ang II mediated by the \textit{AT}_1R. Chronic blockade of the \textit{AT}_2R in rats receiving Ang II resulted in normal arterial pressure but induced a significant aortic hypertrophy and fibrosis. Chronic blockade of the \textit{AT}_2R in Ang II–induced hypertensive rats had no effect on arterial pressure but antagonized the effect of Ang II on arterial hypertrophy and fibrosis, suggesting that in vivo vascular trophic effects of Ang II are at least partially mediated via \textit{AT}_2R in adult normotensive rats.\textsuperscript{86} Nevertheless, in another study conducted in similar conditions, this profibrosis effect of \textit{AT}_1Rs was not found.\textsuperscript{90}

Dzau and coworkers,\textsuperscript{91} used mice lacking \textit{AT}_2 gene (\textit{Agtr2/-}) to test the in vivo roles of the \textit{AT}_2R; they reported that cardiac hypertrophy was induced by suprarenal abdominal aortic banding in 10- to 12-week-old \textit{Agtr2-} and wild-type (\textit{Agtr2+}) mice. Carotid arterial pressure was not different between the strains, although aortic banding increased arterial pressure by \textasciitilde 40 mm Hg. Aortic banding increased the heart-weight/body-weight ratio and the cross-sectional area of cardiomyocytes by 15\%, resulting in comparable cardiomyocyte hypertrophy in the 2 strains. In contrast, coronary arterial thickening and perivascular fibrosis, determined by the media/lumen-area ratio and the collagen/vessel-area ratio, respectively, were 50\% greater in \textit{Agtr2—} than in \textit{Agtr2+} mice after banding. These parameters were similar in sham-operated mice. Radioligand binding studies using the whole heart and immunohistochemistry showed that \textit{AT}_1R expression was limited and localized in the coronary artery and perivascular region. These results suggested that the \textit{AT}_1R mediates an inhibitory effect on coronary arterial remodeling, such as medial hypertrophy and perivascular fibrosis in response to pressure overload, and an activation of the renin-angiotensin system.\textsuperscript{91} In contrast, Inagami et al\textsuperscript{15} developed another strain of mice lacking the \textit{AT}_1R gene (\textit{Agtr2-Y}) to test the in vivo roles of the \textit{AT}_1R. Pressure overload by surgical aortic banding failed to induce left ventricular hypertrophy and fibrosis in \textit{Agtr2-Y} mice, suggesting that \textit{AT}_2R may be responsible for cardiac hypertrophy and perivascular myocardial fibrosis.\textsuperscript{92} The opposite results obtained by these 2 groups are likely in relation with the different genetic background of \textit{Agtr2—} mice used in these studies: Dzau’s group reported coronary arterial remodeling in response to pressure overload in \textit{Agtr2—}/\textit{Y} mice; these mice were back-crossed 6 times into the FVB/N (related to the 129 strain) background\textsuperscript{96} whereas Inagami’s \textit{Agtr2—} mice were back-crossed 9 times on a C57B6 background.\textsuperscript{53}

### Conclusion

Most in vitro studies in cultured cells and in isolated segments of aorta have shown that \textit{AT}_1R stimulation could lead to the production of vasodilating substances, among which NO is the most cited. However, in different organs or in small arteries isolated from different type of tissues, other vasoactive substances may also mediate \textit{AT}_1R-dependent dilation, and sometimes, such as in large renal arteries, \textit{AT}_2R stimulation may lead to a vasoconstriction. Nevertheless, when acutely stimulated, the most probable response expected from \textit{AT}_2R stimulation will be a vasodilation. Thus, in the perspective of a chronic \textit{AT}_1R blockade in patients, overstimulation of \textit{AT}_2Rs might be beneficial, regarding their potential vasodilator effect. Concerning the possible role of \textit{AT}_2Rs in cardiovascular remodeling, the situation is more controversial. In vitro, \textit{AT}_1R stimulation clearly inhibits cardiac and vascular smooth muscle growth and proliferation, stimulates apoptosis, and promotes extra cellular matrix synthesis. In vivo, the situation might be less beneficial if not deleterious; indeed, if chronic \textit{AT}_1R overstimulation would lead to cardiovascular hypertrophy and fibrosis, then the long-term consequences of chronic \textit{AT}_1R blockade and thus \textit{AT}_2R overstimulation require more in-depth analysis.

### References

31. Stromberg C, Naveri L, Saavedra JM. Angiotensin AT2 receptors regulate
29. Tofovic SP, Pong AS, Jackson EK. Effects of angiotensin subtype 1 and
28. Champion HC, Garrison EA, Estrada LS, Potter JM, Kadowitz PJ. Anal-
21. Zhuo J, Dean R, MacGregor D, Alcorn D, Mendelsohn FA. Presence of
24. Cox BE, Word RA, Rosenfeld CR. Angiotensin II receptor characteristics
32. Stromberg C, Naveri L, Saavedra JM. Nonpeptide angiotensin AT1 and
S97.
1371.
J Cardiovasc Pharmacol


28. Champion HC, Garrison EA, Estrada LS, Potter JM, Kadowitz PJ. Anal-
21. Zhuo J, Dean R, MacGregor D, Alcorn D, Mendelsohn FA. Presence of
24. Cox BE, Word RA, Rosenfeld CR. Angiotensin II receptor characteristics
32. Stromberg C, Naveri L, Saavedra JM. Nonpeptide angiotensin AT1 and

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29. Tofovic SP, Pong AS, Jackson EK. Effects of angiotensin subtype 1 and
28. Champion HC, Garrison EA, Estrada LS, Potter JM, Kadowitz PJ. Anal-
21. Zhuo J, Dean R, MacGregor D, Alcorn D, Mendelsohn FA. Presence of
24. Cox BE, Word RA, Rosenfeld CR. Angiotensin II receptor characteristics
32. Stromberg C, Naveri L, Saavedra JM. Nonpeptide angiotensin AT1 and

31. Stromberg C, Naveri L, Saavedra JM. Angiotensin AT2 receptors regulate
29. Tofovic SP, Pong AS, Jackson EK. Effects of angiotensin subtype 1 and
28. Champion HC, Garrison EA, Estrada LS, Potter JM, Kadowitz PJ. Anal-
21. Zhuo J, Dean R, MacGregor D, Alcorn D, Mendelsohn FA. Presence of
24. Cox BE, Word RA, Rosenfeld CR. Angiotensin II receptor characteristics
32. Stromberg C, Naveri L, Saavedra JM. Nonpeptide angiotensin AT1 and

31. Stromberg C, Naveri L, Saavedra JM. Angiotensin AT2 receptors regulate
29. Tofovic SP, Pong AS, Jackson EK. Effects of angiotensin subtype 1 and
28. Champion HC, Garrison EA, Estrada LS, Potter JM, Kadowitz PJ. Anal-
21. Zhuo J, Dean R, MacGregor D, Alcorn D, Mendelsohn FA. Presence of
24. Cox BE, Word RA, Rosenfeld CR. Angiotensin II receptor characteristics
32. Stromberg C, Naveri L, Saavedra JM. Nonpeptide angiotensin AT1 and
68. Tanaka N, Tanaka K, Nagashima Y, Kondo M, Sekihara H. Nitric oxide
69. Matrougui K, Maclouf J, Levy BI, Henrion D. Impaired nitric oxide and
70. Caputo L, Benessiano J, Boulanger CM, Levy BI. Angiotensin II
72. Ichiki T, Kambayashi Y, Inagami T. Differential inducibility of angio-
73. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of
74. Yusuf S, Pepine CJ, Garces C, Poulter H, Salem D, Kostis J, Benedict C,
75. Lamas GA, Pfeffer MA, Hamm P, Wertheimer J, Rouleau JL, Braunwald
76. Geisterfer AA, Peach MJ, Owens GK. Angiotensin II induces hypertro-
77. Berk BC, Vekshtein V, Gordon HM, Tsuda T. Angiotensin II-stimulated
80. van Kleef EM, Fingerle J, Daemen MJ. Angiotensin II-induced pro-
82. Mifune M, Sasamura H, Shimizu-Hirota R, Miyazaki H, Saruta T. An-
83. Levy BI, Benessiano J, Henrion D, Caputo L, Heymes C, Duriez M,
85. Park KW, Dai HB, Comunale ME, Gopal A, Sellke FW. Dilation by
86. Levy BI, Benessiano J, Henrion D, Caputo L, Heymes C, Duriez M,
87. Brilla CG, Janicki JS, Weber KT. Impaired diastolic function and coro-
88. Brilla CG, Janicki JS, Weber KT. Impaired diastolic function and coro-
89. Bartunek J, Weinberg EO, Tajima M, Rohrbach S, Lorell BH. Angioten-
90. Li JS, Touyz RM, Schiffrin EL. Effects of AT1 and AT2 angiotensin
93. Mifune M, Sasamura H, Shimizu-Hirota R, Miyazaki H, Saruta T. An-
94. Levy BI, Benessiano J, Henrion D, Caputo L, Heymes C, Duriez M,
96. Li P, Ferrario CM, Brosnihan KB. Losartan inhibits thromboxane
98. Tsuzuki S, Matoba T, Eguchi S, Inagami T. Angiotensin II type II receptor inhibits cell proliferation and activates tyrosine phosphatase. Hyper-
100. Ichiki T, Kambayashi Y, Inagami T. Differential inducibility of angio-
102. Yusuf S, Pepine CJ, Garces C, Poulter H, Salem D, Kostis J, Benedict C,
108. Park KW, Dai HB, Comunale ME, Gopal A, Sellke FW. Dilation by
109. Levy BI, Benessiano J, Henrion D, Caputo L, Heymes C, Duriez M,
110. Brilla CG, Janicki JS, Weber KT. Impaired diastolic function and coro-
111. Bartunek J, Weinberg EO, Tajima M, Rohrbach S, Lorell BH. Angioten-
113. Mifune M, Sasamura H, Shimizu-Hirota R, Miyazaki H, Saruta T. An-
114. Levy BI, Benessiano J, Henrion D, Caputo L, Heymes C, Duriez M,
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