REVIEW ARTICLE

Cardiovascular effects of the angiotensin type 2 receptor

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Abstract  The angiotensin type 2 receptor, AT2R, has been described as having opposite effects to the angiotensin type 1 receptor, AT1R. Although the quantities of the AT2R found in the adult are low, its expression rises in pathological situations. The AT2R has three major signaling pathways: activation of serine/threonine phosphatases (promoting apoptosis and antioxidant effects), activation of the bradykinin/NO/cGMP pathway (promoting vasodilation), and activation of phospholipase A2 (associated with regulation of potassium currents). The AT2R appears to have effects in vascular remodeling, atherosclerosis prevention and blood pressure lowering (when associated with an AT1R inhibitor). After myocardial infarction, the AT2R appears to decrease infarct size, cardiac hypertrophy and fibrosis, and to improve cardiac function. However, its role in the heart is controversial. In the kidney, the AT2R promotes natriuresis. Until now, treatment directed at the renin-angiotensin-aldosterone system has been based on angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers. The study of the AT2R has been revolutionized by the discovery of a direct agonist, C21, which promises to become part of the treatment of cardiovascular disease.

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PALAVRAS-CHAVE

Recetor da angiotensina tipo 2; Sistema renina-angiotensina-aldosterona;

Efeitos cardiovasculares do receptor tipo 2 da angiotensina

Resumo O recetor da angiotensina do tipo 2, AT2R, tem vindo a ser descrito como tendo acções opostas ao recetor da angiotensina do tipo 1, AT1R. Apesar do AT1R existir em baixas quantidades no adulto, a sua expressão sobe bastante em situações patológicas. O AT2R tem três grandes vias de sinalização: a ativação fosfátases de serina/treonina (promoção da apoptose celular e
Introduction

In the renin–angiotensin–aldosterone system (RAAS), the most widely studied angiotensin (Ang) II receptor is the type 1 receptor, AT1R. This receptor is responsible for most of the effects of RAAS activation, including vasoconstriction, sodium retention, aldosterone release, cell proliferation, cardiac and vascular hypertrophy, and modulation of oxidative stress and inflammation. Ang II also binds to another receptor, AT2R, which was discovered over 20 years ago. However, its functions are still not fully understood. Activation of the AT2R has been reported as having opposite effects to that of the AT1R, and thus appears to have a protective effect in conditions such as hypertension, atherosclerosis and myocardial infarction (MI). Both the AT1R and the AT2R are G protein-coupled receptors (GPCRs) with 34% sequence homology. Various GPCR-interacting proteins (GIPs) also interact with these receptors, binding to the C-terminus. In adults, the AT1R is expressed ubiquitously, while the AT2R is found in low quantities, mainly in the blood vessels, kidneys, adrenal medulla, uterus and ovaries, heart, and certain brain nuclei. However, its expression rises in the above pathological situations. The physiological role of the AT2R in adults is thus insignificant, but in the fetus, the opposite is seen: the AT2R is more abundant, which may be related to its function in general physiological development.

The aim of this review is to describe the functions of the AT2R in the cardiovascular system and to investigate their role in possible treatments.

Signal transduction pathways of the AT2R

The Ang II receptors form homodimers and heterodimers between each other. The homodimers AT1R/AT1R and AT2R/AT2R strengthen the effects of their respective receptors. Formation of the heterodimer AT1R/AT2R reduces the signaling of the AT1R, one way in which the AT1R directly inhibits the effects of the AT2R. The AT2R also forms heterodimers with the bradykinin B2 receptor (B2R), increasing production of nitric oxide (NO). This interaction is important in the kinin/NO/cGMP system.

Once activated, the AT2R has three main signaling pathways: activation of serine/threonine phosphatases, activation of the bradykinin/NO/cGMP pathway, and activation of phospholipase A2.

With regard to phosphatases, the role of the AT2R has been studied in the activation of MAP kinase phosphatase (MKP-1), protein phosphatase 2 (PP2A) and SH2 domain-containing tyrosine phosphatase (SHP-1). Activation of MKP-1 and PP2A by the AT2R results in inhibition of ERK1/2 (ERK1/2), inducing apoptosis. When activated, SHP-1 inhibits ERK1/2 and NAD(P)H oxidase (stimulated by the AT1R), and is thus part of the endothelium’s oxidative stress defense.

Activation of the bradykinin/NO/cGMP pathway is associated with vasodilation. When activated, the AT2R stimulates the B2R receptor, which in turn induces phosphorylation of endothelial nitric oxide synthase (eNOS) at Ser633 and Ser1177 via a PKA-mediated signaling pathway. NO production is thus increased, activating guanylate cyclase (sGC), which synthesizes cGMP from GTP, in turn promoting vasodilation. Although these mechanisms have been described before, the role of the AT2R in regulation of blood pressure (BP) is still the subject of debate.

The AT2R also stimulates phospholipase A2 (PLA2) activity and arachidonic acid (AA) formation; the latter regulates potassium currents and can lead to cell hyperpolarization and reduced excitability. This effect appears to be particularly important in reducing sympathetic activity.

Gilluly et al. described an alternative signaling pathway to the bradykinin/NO/cGMP system in vascular smooth muscle cells that culminates in phosphorylation and inactivation of RhoA on Ser188, leading to vasodilation (Figure 2). Ste20-related kinase (SLK) is responsible for this phosphorylation, which is independent of eNOS, PKA and PKG. The effect is weakened when SLK is phosphorylated, hence SLK phosphorylates RhoA when in the dephosphorylated state. Meanwhile, casein kinase 2 (CK2) is responsible for the basal phosphorylation of SLK. The role of the AT2R in this pathway is thus to reduce the activity of CK2 in order to increase the quantity of dephosphorylated SLK. Since CK2 is active when phosphorylated, the AT2R achieves its
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Figure 1  Main signaling pathways of the AT$_2$R. Activation of the receptor leads to three pathways: activation of serine/threonine phosphatases (1); activation of phospholipase A2 (2); and activation of the bradykinin/NO/cGMP pathway (3). AA: arachidonic acid; Ang II: angiotensin II; AT$_2$R: angiotensin receptor type 2; B$_2$R: bradykinin receptor B2; cGMP: cyclic guanosine monophosphate; eNOS: endothelial nitric oxide synthase; ERK1/2: extracellular-regulated kinase 1 and 2; GTP: guanosine triphosphate; MKP-1: MAP kinase phosphatase; NO: nitric oxide; PKA: protein kinase A; PLA2: phospholipase A2; PP2: protein phosphatase 2; sGC: soluble guanylate cyclase; SHP-1: SH2 domain-containing tyrosine phosphatase.

Figure produced using Servier Medical Art (http://www.servier.co.uk/medical-art-gallery/).

inhibitory effect through SHP-1, which dephosphorylates CK2.

The AT$_2$R is also involved in anti-inflammatory pathways that reduce the expression of interleukin-6 (IL-6), mainly in stimulation of serine/threonine phosphatases and in the synthesis of AA, which then produces the metabolite 11,12-EET, part of the inflammatory pathway. These two processes converge to reduce the activity of nuclear factor κB (NF-κB), which in turn reduces IL-6.

It should be noted that these receptors can be activated independently of binding to Ang II. The AT$_1$R may be activated solely by mechanical stress, leading to increased expression of calcineurin which, in turn, causes cardiac hypertrophy, while in a study of mouse ovary cells, Miura and Karnik showed that the AT$_2$R does not need angiotensin to induce apoptosis. It is now accepted that some AT$_2$Rs are constitutively active in the form of homooligomers. These characteristics of the Ang II receptors are particularly relevant in drug treatments, as discussed below.

The AT$_2$R and its agonist C21

The first studies on the AT$_2$R were all indirect, some involving selective activation of the AT$_2$R by supplying Ang II in the presence of an AT$_1$R inhibitor II, and some using an AT$_2$R antagonist such as PD123319 to study the effects of disabling this receptor. However, the latter approach has the disadvantage that PD123319 lacks specificity when applied at high doses. Other studies have used mice genetically engineered to under- or over-express the AT$_2$R gene.

The most direct way to study the AT$_2$R is to use a specific agonist. Until 2004 the best available agonist was CGP42112A, but this ligand is rapidly degraded in vivo and has antagonistic as well as agonistic properties. However,
in that year, Wan et al.\textsuperscript{26} reported the design and synthesis of a new agonist, compound 21 (C21), which has revolutionized the study of the AT$_2$R. This non-peptide agonist, which can be administered orally, allows direct in vitro and in vivo stimulation of the AT$_2$R without affecting the AT$_1$R.

**Vascular effects of the AT$_2$R**

Ang II regulates various processes involved in vascular pathophysiology, including growth and apoptosis of vascular cells, migration of vascular smooth muscle cells, inflammatory responses and extracellular matrix remodeling.\textsuperscript{13} Ang II can bind to the AT$_1$R or to the AT$_2$R, which have opposite effects. For example, it has been shown that a deletion in the AT$_2$R gene is associated with higher BP, reflecting the absence of AT$_2$R-related vasodilation.\textsuperscript{4,27} A study by Savoia et al.\textsuperscript{28} showed, for the first time, upregulation of the AT$_2$R in peripheral arteries of hypertensive diabetic patients treated with the AT$_2$R blocker valsartan for one year. This increase in the AT$_2$R was associated with lower blood pressure in these patients in a dose-dependent fashion. The authors confirmed this effect by exposing samples of precontracted peripheral arteries ex vivo to valsartan; the result was again increased AT$_2$R expression and vasodilation. This increase was seen mainly in the media of the vessel wall, and so the authors hypothesize that the AT$_2$R stimulates vasodilation directly in vascular smooth muscle cells via RhoA, as described above.

Zhang et al.\textsuperscript{29} studied the functions of the AT$_1$R and the AT$_2$R in the coronary circulation and concluded that stimulation of the AT$_1$R evoked vasoconstriction and stimulation of the AT$_2$R induced vasodilation. Removal of endothelium or administration of an NO synthase inhibitor abolished the vasodilatory response of the AT$_2$R. The authors also found that superoxide production via AT$_1$R activation of NAD(P)H oxidase, as described above, inhibited vasodilation, the superoxide reacting with NO and thus acting as an NO scavenger.

The AT$_2$R is abundant in the fetus, and it has therefore been argued that it plays a role in normal vascular development and growth.\textsuperscript{13} AT$_2$R expression is linked to fetal angiogenesis and influences the phenotype of vascular smooth muscle cells by altering ERK activity.\textsuperscript{28} AT$_2$R expression peaks towards the end of gestation; this is linked to...
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reduced DNA synthesis in the aorta. Normal vascular differentiation is thus achieved by the opposing actions of the AT1R and the AT2R. In adults, the AT2R continues to play a part in vascular remodeling, inducing apoptosis and inhibiting cell proliferation (which is promoted by the AT1R). This is particularly evident following carotid artery balloon injury, following which in-vivo transfer of the AT2R gene significantly attenuates neointimal formation. Dysregulation of this remodeling process is associated with pathological states. For example, loss of AT2R expression accelerates the development and rupture of aortic aneurysms in a mouse model of Marfan syndrome. In these mice, an AT2R inhibitor (the angiotensin receptor blocker [ARB] losartan) slowed aneurysm progression but full protection required intact AT2R signaling. There are also indications that the AT2R plays a part in protecting against vascular hypertrophy. Following the discovery of C21, new light has been shed on the vascular effects of the AT2R. One idea – that AT2R-related vasodilation reduces BP – has been disproved by new research: administration of C21 does not by itself reduce BP in either normotensive or hypertensive animals. The only study to show a fall in BP was the one that first described C21, in hypertensive rats, and furthermore the animals were anesthetized, which would make them more sensitive to pharmacological modulation of the RAAS. Since the predominance of the AT2R hinders investigation of the effects of direct AT2R stimulation in vivo, Bosnyak et al. administered C21 together with a low dose of the ARB candesartan, which does not lower BP by itself, and saw a significant BP fall in hypertensive rats. This response was abolished by administration of an AT1R antagonist. When a high-dose ARB is added to C21 there is no additional effect on BP beyond that of the ARB alone. These studies with C21 confirm that the AT2R mainly confers protection against vascular injury. Rehman et al. showed in hypertensive rats that C21 alone reduces vascular stiffness, aortic medial collagen content and the coronary perivascular collagen:media cross-sectional area ratio. Paulis et al. studied the effects of C21 independently of NO, using an NO synthase inhibitor (l-NAME) in all experimental groups except controls; they concluded that chronic AT2R stimulation prevented aortic stiffening and collagen accumulation without preventing hypertension.

Effects of the AT2R on cardiac structure

The two Ang II receptors are also involved in remodeling in the heart, but there is disagreement as to the underlying processes. Under normal conditions the AT2R is expressed in the heart at very low levels, but in pathological conditions such as hypertension or MI its expression increases greatly, to the extent that its action predominates over that of the AT1R. Most of the controversy about the actions of the AT2R has arisen from studies of cardiac hypertrophy, fibrosis and post-MI cardiac function. Post-MI remodeling has an acute phase of infarct expansion, followed by hypertrophy and interstitial fibrosis of cardiomyocytes that did not undergo ischemia. Most studies indicate that the AT2R has a beneficial effect in the heart. The main findings of a review by Johren et al., dating from 2004 (before the discovery of C21), of studies in AT1R knockout mice, were that in the myocardium, deletion of the AT2R gene leads to increased AT1R expression and thus AT1R-mediated cell proliferation, and increased cardiac hypertrophy, reduced survival and increased left ventricular (LV) dilatation after MI. Among the disagreements in this field, some studies indicate that knocking out the AT2R promotes perivascular fibrosis, while others come to exactly the opposite conclusion. Other studies followed the review by Johren et al., but the controversy continued. Table 1 presents a summary of more recent research. Of particular note is Voros et al., who compared five groups of mice and found that both blockade of the AT1R and overexpression of the AT2R had beneficial effects on cardiac remodeling, and the AT1R knockout transgenic mice with AT2R overexpression consistently had higher ejection fraction, smaller LV end-diastolic volume and less fibrosis in regions adjacent to the infarct. However, other studies contradict the idea that the AT2R has protective effects in the heart. In a study by Tschope et al., AT2R knockout mice showed no differences from controls after MI in LV systolic and diastolic function or in fibrosis or remodeling of the extracellular matrix. The authors concluded that ischemia-induced hypertrophy and fibrosis are independent of the AT1R. Van Esch et al. showed that the absence of the AT2R did not enhance the effects of the AT1R, while in the absence of the AT1R, the cardiac effects mediated by the AT2R were not observed.

The first study with C21 in this area, by Kaschina et al., concluded that AT1R stimulation may improve post-MI systolic and diastolic function, and also observed activation of anti-inflammatory mechanisms that afford some degree of cardiac protection. However, even after the discovery of C21, the controversy continues; a more recent study by Jehle et al. concluded that direct stimulation of the AT1R does not attenuate post-MI LV remodeling and in fact has adverse effects, particularly increased LV end-systolic and end-diastolic volume, compared to the group treated with an ARB.

Effects of the AT2R on the inflammatory response

Ang II is considered a proinflammatory agent; binding to the AT1R triggers an inflammatory response. Endothelial dysfunction is characterized by impaired endothelium-dependent vasodilation, which is preceded by a series of structural changes in the vessel wall, including increases in adhesion molecules, number of monocytes and their adhesion to the endothelium, inflammation, and vascular smooth muscle fibers. These changes are linked to the progression of pathological conditions such as atherosclerosis, which are associated with a sharp decline in vasodilatory capacity, the main factor in which is reduced NO availability.

However, it has been suggested that the AT2R has anti-inflammatory effects. Sales et al. demonstrated increased AT1R expression at the site of atherosclerotic lesions. AT2R knockout mice had increased macrophages, vascular smooth muscle cells and collagen in plaques, and increased AT2R...
Effects of the AT$_2$R on the kidney

The extensive role of the AT$_2$R in the kidney is beyond the scope of this review, and so only those effects that are directly related to cardiovascular function will be described.

The AT$_2$R is expressed in the kidney at high levels in the fetus but at very low levels in the adult. Mutations in the AT$_2$R gene are associated with congenital abnormalities of the kidney and urinary tract, and absence of the receptor is linked to renal diseases such as diabetic nephropathy.

### Table 1  Effects of the AT$_2$R after myocardial infarction and in heart failure.

<table>
<thead>
<tr>
<th>Beneficial effects after MI (compared to controls)</th>
<th>Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced infarct size</td>
<td>44,70</td>
</tr>
<tr>
<td>Increased maximum and minimum dP/dt</td>
<td>44,70,71</td>
</tr>
<tr>
<td>Increased ejection fraction</td>
<td>44,70-73</td>
</tr>
<tr>
<td>Increased contractility</td>
<td>44</td>
</tr>
<tr>
<td>Reduced LV end-systolic volume</td>
<td>41,72,73</td>
</tr>
<tr>
<td>Reduced LV end-diastolic volume</td>
<td>41,72,73</td>
</tr>
<tr>
<td>Reduced LV end-diastolic pressure</td>
<td>44,71</td>
</tr>
<tr>
<td>Reduced left atrial pressure</td>
<td>70</td>
</tr>
<tr>
<td>Reduced LV hypertrophy</td>
<td>71</td>
</tr>
<tr>
<td>Reduced LV/body weight ratio</td>
<td>74</td>
</tr>
<tr>
<td>Reduced lung/body weight ratio</td>
<td>74</td>
</tr>
<tr>
<td>Reduced interstitial fibrosis in regions adjacent to the infarct</td>
<td>71</td>
</tr>
<tr>
<td>Reduced levels of monocyte chemoattractant protein-1, myeloperoxidase and interleukins (anti-inflammatory effects)</td>
<td>44</td>
</tr>
</tbody>
</table>

### Absence of effects or deleterious effects after MI (compared to controls)

- No changes in systolic or diastolic function
- No changes in fibrosis and extracellular matrix
- Increased LV end-systolic and end-diastolic volume
- No inhibition of the effects of the AT$_2$R

### Beneficial effects in HF (compared to controls)

- Increased maximum and minimum dP/dt
- Increased ejection fraction
- Reduced mean pulmonary artery pressure
- Reduced LV end-systolic volume
- Reduced LV end-diastolic volume
- Reduced LV end-diastolic pressure
- Reduced aldehydes (a marker of oxidative stress)

### Study approach

- AT$_2$R knockout mice
- Transgenic mice overexpressing AT$_2$R vs. controls
- Wild-type mice+ARB vs. AT$_2$R knockout mice+ARB
- AT$_2$R knockout mice+AT$_2$R wild-type mice vs. AT$_2$R knockout mice+AT$_2$R wild-type
- AT$_2$R promoter injected via an adenoviral vector into left ventricle of rats
- AT$_2$R blockade with ARBs in dogs
- Wild-type mice vs. wild-type mice+ARB vs. transgenic mice overexpressing AT$_2$R vs. transgenic mice overexpressing AT$_2$R+ARB vs. transgenic mice overexpressing AT$_2$R and AT$_2$R knockout
- Treatment with C21 in rats (0.01, 0.03, 0.3 mg/kg/day)
- Mice treated with C21 (0.3 mg/kg/day) vs. treated with ARB vs. untreated controls

ARB: angiotensin receptor blocker; HF: heart failure; MI: myocardial infarction.

*Refs. 70 and 75 did not study the effects of the AT$_2$R, but of AT$_2$R antagonism with ARBs. However, the authors concluded that part of the effects of the ARBs were due to increased AT$_2$R activation since this was overexpressed. Studies would benefit from the inclusion of a group specifically designed to study the AT$_2$R, such as double knockout mice, transgenic mice overexpressing the AT$_2$R, or a direct AT$_2$R agonist.*

Figure 3  Promotion of natriuresis via activation of the AT$_2$R by Ang III. Ang II does not promote natriuresis until it has been converted to Ang III by APA. Ang III is then converted by APN to Ang IV, which does not trigger natriuresis. APA can be inhibited by PC-18 and APN by EC-33. AT$_2$R: angiotensin receptor type 2; Ang II: angiotensin II; Ang III: angiotensin III; Ang IV: angiotensin IV; APA: aminopeptidase A; APN: aminopeptidase N.

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Figure 4  AT₂R signaling pathway via activation of PLZF. Following activation of the AT₂R, PLZF binds to its C-terminus and both undergo endocytosis. The vesicle translocates to the nucleus, which PLZF enters, while the AT₂R remains in the perinuclear region. PLZF promotes the transcription of PI3K-p85α, which is associated with cardiac hypertrophy. AT₂R: angiotensin receptor type 2; Ang II: angiotensin II; PLZF: promyelocytic zinc finger protein; PI3K p85α: phosphatidylinositol-3 kinase-p85α.

Figure produced using Servier Medical Art (http://www.servier.co.uk/medical-art-gallery/).

Inhibition of the AT₁R promotes natriuresis, an effect that is abolished when an AT₂R blocker is administered, demonstrating that natriuresis is one of the effects of the AT₂R. However, direct binding of Ang II to the AT₂R does not have this effect; Ang II must first be converted to Ang III, which then binds to the AT₂R, resulting in natriuresis. AT₂R is converted to Ang III by aminopeptidase A (APA), while Ang III is converted to Ang IV by aminopeptidase N (APN). Thus, in the presence of an AT₁R blocker, administration of Ang II together with PC-18, a specific inhibitor of APN, results in natriuresis, since more Ang III binds to the AT₂R. The opposite occurs when Ang II is administered with EC-33, a selective APA inhibitor, which reduces Ang III and hence natriuresis (Figure 3). AT₂R-mediated natriuresis occurs via activation of the kinin/NO/cGMP system in the renal proximal tubule. Natriuresis is also triggered by AT₂R activation in the thick ascending limb of Henle, although it is not known whether this is due to binding to Ang III. The underlying mechanism also involves the production of NO, which inhibits the Na⁺/K⁺/2Cl⁻ cotransporter, thus increasing sodium excretion.

The AT₂R and the nervous system

The Ang II receptors also have opposing effects in the nervous system. Their main role is in regulating the sympathetic nervous system, which the AT₁R stimulates and the AT₂R inhibits. It is thus logical that AT₂R knockout mice should have higher BP. The receptors that control sympathetic tone are located in the rostral ventrolateral medulla, where AT₂R overexpression reduces noradrenaline excretion.

AT₂R ligands (GPCR-interacting proteins)

AT₂ receptor-interacting protein (ATIP) binds selectively to the C-terminus and does not bind to the AT₁R. It cooperates with the AT₂R to transinactivate receptor tyrosine...
kinases that are independent of G proteins. For example, it inhibits activation of epidermal growth factor receptor (EGFR)-induced ERK2, thus complementing the proapoptotic effects of the AT1R. The AT1R does not need to be activated for ATIP to bind to it.

AT1R binding protein of 50 kDa (ATBP50) is a Golgi membrane-associated protein that regulates the transport of the AT1R to the cell membrane by binding to its C-terminus. Downregulation of ATBP50 decreases the antiproliferative effects of the receptor.

Promyelocytic zinc finger protein (PLZF) provides another signaling mechanism for the AT1R, binding to its C-terminus, as described by Senbonmatsu et al. (Figure 4). After activation by Ang II, the AT1R binds to PLZF and both translocate to the nucleus. The AT1R remains in the perinuclear region while PLZF enters the nucleus, where it promotes transcription of the kinase PI3K p85α, which is associated with increased protein synthesis and cardiomyocyte growth. This pathway may explain the contradictory findings concerning the role of the AT1R in cardiac hypertrophy.

**Therapeutic approaches**

The two main drug classes used for modulating the RAAS and treating related pathological conditions are ARBs and angiotensin-converting enzyme (ACE) inhibitors. It has been suggested, in view of the beneficial effects of the AT1R revealed by recent research, that ARBs have greater therapeutic potential than ACE inhibitors, since the latter reduce Ang II levels and thus the activity of the AT1R. Although ARBs should theoretically be more effective, they are still far from being validated as the first-line mechanical stress.

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**Conclusion**

The AT1R has been the subject of considerable controversy since its discovery, with contradictory findings that make its actions difficult to fully understand. However, as more factors influencing its signaling pathways and more proteins that can bind to the receptor have been discovered, its functions are becoming clearer. There is now general agreement that it has opposite effects to the AT1R in most tissues, but whether this is sufficient to conclude that it has protective effects in cardiovascular disease is still debatable. New studies, particularly on the antagonist C21, promise to help dispel the uncertainties concerning the
AT_R. Novel therapies may soon be available that promote the AT_R’s protective effects and reduce the consequences of cardiovascular disease, including atherosclerosis, MI and heart failure. The vistas that have opened up through the study of the AT_R hold out the hope of new and better treatments.

Conflicts of interest

The authors have no conflicts of interest to declare.

References


