

Angiotensin II type-2 receptor-specific effects on the cardiovascular system

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Abstract: The renin-angiotensin system (RAS) is intricately involved in cardiovascular homeostasis. It is well known that angiotensin II, the key effector in RAS, contributes to a range of cardiovascular pathologies and diseases via angiotensin II type-1 receptor (AT1R) activation. However, the role of angiotensin II type-2 receptor (AT2R) regulation is less well understood. Recent studies describe the role of the AT2R on cardiovascular function in normal and pathologic conditions. The data describe an important role of AT2R in blood pressure regulation, cardiac hypertrophy and fibrosis, myocardial infarction and vascular homeostasis.

Key Words: Rennin-angiotensin system; AT2 receptor; cardiovascular disease



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Introduction

The renin-angiotensin system (RAS) plays a critical role in cardiovascular homeostasis. The principle effector of this system is angiotensin II (Ang II), which acts at least four different receptors subtypes (AT1R-4). AT1R and AT2R receptors cDNAs have been cloned successfully almost two decade ago (1). Most of the classic cardiovascular effects of the Ang II, including blood pressure regulation, promotion of inflammatory responses, arterial wall thickening, and myocardial fibrosis, have been demonstrated to be mediated by the AT1R. The AT2R is clearly distinct from the AT1R in molecular weight, tissue-specific expression, and signaling mechanisms. Past studies have demonstrated that AT2R may counter-regulate AT1R function. However, the specific role of the AT2R is incompletely understood, with contradictory results in the various studies. As there is an increasing number of drugs with effect on the RAS, including angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB), used in clinical practice, it becomes essential to clarify the specific function of the AT2R.

Gene location and gene polymorphisms

The genes encoding the AT2R are localized on human chromosome Xq22-q2 (1). The genomic DNA of the human AT2R consists of three exons with an uninterrupted coding region being confined to the third exon (2). Both AT1R and AT2R belong to the seven-transmembrane domain superfamily of receptors, and they share 34% of their nucleic acid sequence. Human AT2R molecular weight is 41 kDa, with 363 amino-acids (3). Mouse and human AT2R both have more than 92% homology with the rat homolog (4). Several single nucleotide polymorphic (SNP) variants of human AT2R are known. A study about genetic variants of AT2R (1675A>G and 3123C>A) and cardiovascular risk in 2579 subjects suggests there is no association between coronary heart disease (CHD) risk and 1675A versus 1675G SNP variants. However, the 1675A genotype is associated with a higher risk of CHD in subjects with systolic hypertension, whereas 1675G carriers were protected from the effect of hypertension, with no association between increasing risk and increasing SBP. Furthermore, individuals carrying both 3123A and 1675A

SNPs have a tenfold greater risk of CHD than 3123A and 1675G haplotypes (5). Other studies have focused on the association between polymorphism of AT2R 1332A>G SNPs and cardiovascular disease and conclude that 1332G SNP variants have a higher prevalence of hypertension (6) and premature coronary artery disease (7).

AT2R expression

The AT2 receptors are highly expressed in fetal tissues, although their expression dramatically decreases after birth, being restricted to a few organs, including the cardiovascular system (8), suggesting it might play an important role in fetal cardiovascular development. But recent data using Western blot technique to measure total AT2R protein in tissue, showed adult rats exhibited a higher AT2R protein level compared with foetus or neonates in the brainstem, liver and kidney tissue (9). In the cardiovascular system, AT2R expresses in the heart (cardiomyocytes (10), cardiac fibroblasts (11)), and vessels (aorta (12), coronary artery (13), resistant artery (14)). In pathological conditions, including inflammation, congestive heart failure, hypertension, myocardial ischemia and vascular injury, AT2R can be regulated (8). For example, a previous study (12) demonstrated that AT2R expression was increased in segments from diseased compared with control aortas, whereas AT2R was down-regulated in resistance arteries of hypertensive subjects compared with adult SHR and WKY rats. After RAS specific and nonspecific antihypertensive treatment, AT2R expression and vasodilator functions could be reversed (14). These data suggest complex local regulation of AT2R expression, which may mediate vascular growth, development, and repair (*Figure 1*).

Vasodilation

It is generally accepted that Ang II mediate vasodilation through the AT2R pathway, opposing the vasoconstrictor action of AT1R. Studies in the mid to late 1990s indicated links between AT2R and vasodilators including bradykinin(BK), nitric oxide(NO), and guanosine cyclic 3', 5'-monophosphate (cGMP) (15-17). Recently, the AT2 receptor and bradykinin B2 receptor were shown to form a stable functional heterodimer, which leads to increased NO and cGMP production (18). These discoveries turned attention to the possibility that the AT2R may mediate vasodilation. However, it is difficult to elicit a vasodilatory

response directly in animal models, because AT2R expression is extremely lower than AT1R. To unmask the vasodilator action of AT2R, experiments have focused on eliminating the vasoconstrictor action of AT1R with an AT1R blocker before and during AT2R stimulation. Most studies demonstrated that the AT2R mediate vasodilator response in animal models and human resistance vessels when AT1R were blocked in acute and chronic experiments. For instant, in the presence of AT1R blockade, AngII induced endothelial AT2R cause vasodilation through local production of BK in resistant arteries of rat mesentery in a flow-dependent manner (19). In hypertensive rats, chronic AT1R blockade is also associated with an reversed vasomotor response to Ang II via AT2R mediated NO production (20). In a study by Savoia *et al.*, AT2R expression was up-regulated and mediated vasodilation during selective AT1R blockade for 1 year in resistance vessels of high-risk patients (21). Batenburg *et al.* (13), studying human coronary microarteries, demonstrated that Ang II-induced contraction was potentiated by AT2 receptor blockade and this phenomenon was abolished by icatibant, L-NAME, or removal of the endothelium. This study demonstrated functional AT2 vasodilator receptors in the coronary microcirculation that use a BK-NO-cGMP signaling pathway. In addition to resistance vessels, the vasodilator role of AT2R in capacitance vessels was confirmed in recent studies. Yayama *et al.* tested the contractile response of thoracic aorta to AngII under pressure-overload by abdominal aortic banding in rats. An AT2 receptor antagonist could increase the Ang II responsiveness (22). Subsequent studies used an AT2 receptor activator to directly investigate the role of AT2R *in vitro*. Compound21, a newly created non-peptide AT2R agonist, evoked dose-dependent vasorelaxation in aortic and mesenteric vessels, abolished by PD123319 (23). Moltzer *et al.* found that PD123319 enhanced the constrictive effects of Ang II and III in coronary arteries in Wistar rats, but did not alter the responses in SHRs. In fact, the coronary constrictor effects of Ang II and III in SHRs in the absence of PD123319 were as large as their coronary constrictor effects in Wistar rats in the presence of PD123319. This suggests that the main reason for the enhanced coronary constrictor effects in SHRs is the lack of counterregulatory AT2 receptor-mediated coronary vasodilation (24). In contrast a study by You *et al.* showed that AT2R stimulation induces a vasoconstriction in untreated SHR resistance arteries. Specific or non-specific anti-hypertensive treatments for four weeks may restore vasodilator function (14).

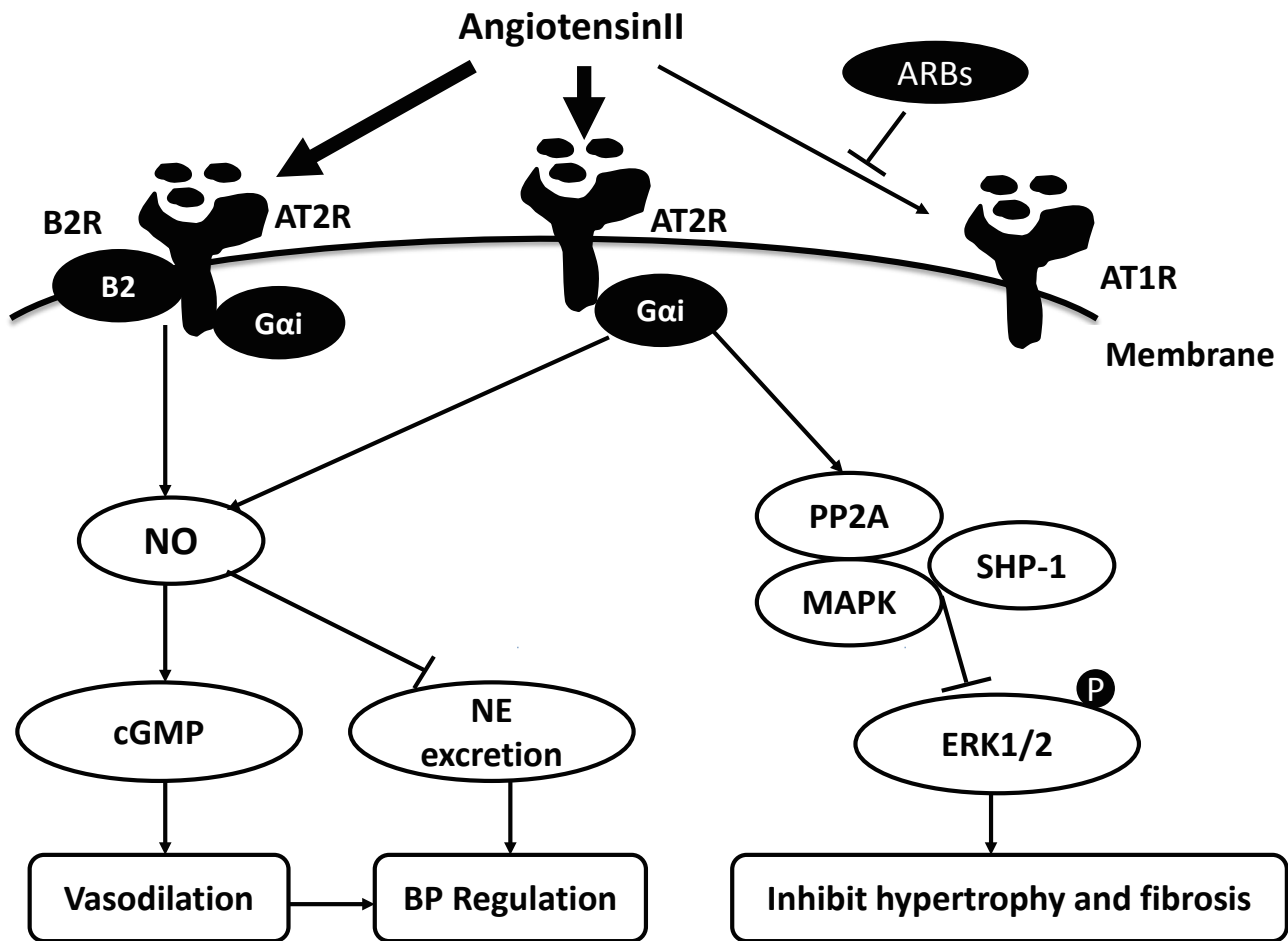


Figure 1 Putative mechanism underlying AT2R's function in cardiovascular diseases. AT2R, Angiotensin II Type-2 Receptor; AT1R, Angiotensin II Type-1 Receptor; ARBs, Angiotensin Receptor Blockers; B2R, Bradykinin B2 Receptor; G α i, G protein; NO, Nitric Oxide; cGMP, 3'-5'-cyclic guanosine monophosphate; NE, Norepinephrine; PP2A, Protein phosphatase 2A; MAPK, Mitogen-activated Protein Kinase; SHP-1, Src homology region 2 domaincontaining phosphatase; ERK1/2, Extracellular signal-regulated kinases 1 and 2

Blood pressure regulation

In the mid 1990s, Scheuer *et al.* (25) found that during AT1R blockade, Ang II and AngIII cause a hypotensive response, which was eliminated by AT2R antagonist. This observation demonstrated that the AT2 receptors mediate a depressor response to Angiotensin. AT2R knockout models (AT2R-KO) developed normal blood pressure, but showed an increased vasopressor response after injection of Ang II (26), while chronic infusion of Ang II into mice with overexpression of AT2-TG mice completely abolished the AT1-mediated pressor effect (27). A recent study demonstrated that low dose of Ang II may significantly reduce BP in female rats through the AT2R pathway (28)

and PD123319 treatment of obese Zucker rats raised mean arterial pressure by 13 mmHg (29), while Compund21 may reduce blood pressure in SHR when combined with the AT1R antagonist, candesartan (23). It is generally accepted that AT2R contribute to maintenance of blood pressure by controlling the vascular tone through vasodilation. Recently, studies suggested a potential inhibitory effect of stimulating central AT2Rs on blood pressure, which is likely mediated by sympatho-inhibition. As mentioned before, AT2R shows high expression in brainstem, which may mediate AngII function in central nervous system. Gao *et al.* (30) demonstrated that overexpression of AT2R protein in the rostral ventrolateral medulla (RVLM; a primary brainstem nucleus related to the control of sympathetic outflow)

suppressed norepinephrine excretion and reduced arterial blood pressure in normal rats. In addition, chronic infusion of Compund 21 decreased nocturnal norepinephrine (NE) excretion and blood pressure via a nNOS/NO signaling pathway within PVN (Paraventricular nucleus) and RVLN. In summary, AT2R is involved in blood pressure regulation, but the detailed mechanism are incompletely understood.

Inhibition of myocardial hypertrophy and fibrosis

AngII mediate cell proliferation and ACEI inhibit left ventricular hypertrophy independent of the effect on blood pressure. Previous studies have examined the role of AT1R and AT2R in myocardial hypertrophy and fibrosis. In early studies, Booz *et al.* have shown that angiotensin II stimulates increased hypertrophy in isolated neonatal rat cardiac myocytes, measured by an increasing protein/DNA ratio. This action was blocked by specific AT1 receptor antagonists, while AT2 antagonists enhanced Ang II stimulation of protein synthesis (10). Similar results were shown in aged rats: AT1R antagonists significantly reduced cardiac hypertrophy and fibrosis while these structural changes were reversed by concomitant AT2 antagonist administration (31). Persistent cardiac overexpression of the AT2R resulted in an 85% attenuation of left ventricular wall thickness, 91% attenuation of heart weight to body weight ratios, and a 43% decrease in myocardial fibrosis induced by angiotensin infusion in rats (32). Aortic banding in mice with overexpression of AT2R-TG resulted in reduction of left ventricular hypertrophy as demonstrated by decreased cardiomyocyte diameter and collagen content (33). These studies clearly demonstrate that AT2R plays a functional role in the cardiac hypertrophic and fibrosis process *in vivo*, and AT2R may mediate these functions by selectively regulating the expression of growth-promoting and growth-inhibiting factors. However, contradictory results were demonstrated in AT2R-KO mice. Ang II elevated systolic blood pressure to comparable levels in AT2R-KO and WT mice. WT mice developed prominent concentric cardiac hypertrophy and prominent fibrosis while there was no significant change in AT2R-KO mice (34). D'Amore *et al.* used recombinant adenoviruses expressing different ratios of rat AT1R and AT2R to infect cardiomyocytes cultured from neonatal rat hearts to study their combined effects on hypertrophy of the cells in response to Ang II. The results showed that basal and Ang II-mediated hypertrophy was increased with the amplified expression of the AT2R and this was unaffected by Ang II stimulation or the classic AT2

antagonists, and Ang II stimulation promoted hypertrophy via activation of mitogen-activated protein kinases (MAPKs) (35). The authors concluded that the AT2R could play a deleterious role in cardiac hypertrophy. Recently, Ha *et al.* found septal hypertrophy and upregulated AT2R in young rats with early obesity. However, it is not clear whether septal hypertrophy was associated with an increase of AT2R, although the author regarded AT2R as a cardioprotective effector (36).

Inhibition of arterial hypertrophy and fibrosis

As mentioned before, AT2R is highly expressed in the fetal heart and vessel system, declines rapidly after birth, but may increase after vascular injury. This suggests an important role in the remodeling of vascular tissue. In 1996, Levy *et al.* showed that long and chronic blockade of AT2R 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 AT2R could play a deleterious role in the process of vascular remodeling (37). However, subsequent data showed AT2R may protect the function of vascular tissue. Brede *et al.* compared isolated femoral arteries from AT2R-KO mice and WT mice, and demonstrated enhanced vasoconstriction of femoral arteries from AT2R-KO mice to angiotensin II. Morphometric analysis of large and small femoral arteries revealed significant hypertrophy of smooth muscle cells in the media (38). Similar results were also found in aged rats. Jones *et al.* showed that cardiac hypertrophy and fibrosis, and aortic hypertrophy were all significantly reduced by candesartan cilexetil and these structural changes were reversed by concomitant PD123319 administration, which demonstrate AT2R may inhibit cardiovascular hypertrophy and fibrosis in the ageing heart and vasculature (31). Okumura *et al.* found that arterial AT2R expression and plasma estrogen level were lower in aged than young female WT mice, and no significant change of AT1R between aged female mice and young female mice (39). In addition, estrogen supplementation and ARB treatment showed synergistic inhibition of atherosclerosis (40). It has therefore been suggested that AT2R may be involved in the response to estrogen and improvement of vascular remodeling in the aged female group. Recently, Habashi *et al.* showed that loss of AT2 expression accelerates the aberrant growth and rupture of the aorta in a mouse model of Marfan syndrome (MFS). ARB was more effective than ACEI to arrest

aneurysm progression in the mice. Those data highlight the protective role of AT2R with potential impact on future choice of therapies in MFS (41). The signal pathway for antiproliferation and antigrowth function of AT2R is not clear. A lot of evidence demonstrated that extracellular signal-regulated kinases 1 and 2 (ERK1/2) were desphosphorylated when AT2R activation (42), and Src homology region 2 domain-containing phosphatase (SHP-1), MAPKs, and protein phosphatase 2A (PP2A) may involved in the process of activation (43-45). But D'Amore *et al.*'s study showed that adenovirus-mediated over-expression of AT2 receptors in neonatal cardiomyocytes increased growth in a constitutive and ERK1/2-independent manner (35).

Cardiac protective function after myocardial infarction

In an early study, Jalowy *et al.* found that the AT1R antagonist candesartan reduced the infarct size in pigs. Surprisingly, this protective function could be abolished after pretreatment with an AT2R antagonist (46). The author suggested that AT2R activation may be involved in the therapeutic effect of the candesartan. Yang *et al.* studied cardiac function at baseline and after myocardial infarction (MI) in mice with overexpression of AT2-TG compared with WT mice. The study demonstrated that AT2-TG mice developed a significantly smaller end-systolic volume index (ESVI) and higher ejection (EF) fraction than WT mice. There were no differences on heart rate, blood pressure and stroke volume after MI, but ESVI remained lower and EF higher at each time point up to day 28 post-MI. At day 28, LV wall thickness, filling pressures, and contractile function were higher in AT2-TG than WT mice (47). In contrast to overexpression of AT2R, Brede *et al.* studied AT2R-KO mice after myocardial infarction, which led to increases in heart: body weight ratios and myocardial cross-sectional areas compared with WT mice. The AT2R-KO mice had down-regulation of myocardial endothelial nitric oxide synthase and reduced cGMP levels (48). Adachi *et al.* also demonstrated that AT2 receptor deficiency exacerbates short-term death rates and heart failure after experimental AMI in AT2-KO mice (49). Oishi *et al.* (50) demonstrated that AT2R-KO mice have greater cardiac remodeling/hypertrophy, systolic and diastolic dysfunction, and increased mortality after MI compared with WT mice. In contrast to the previous study, the cardioprotective role of the AT2 receptor was independent of myocyte hypertrophy.

Furthermore, Compound 21, given for 7 days, can improve the ventricular function and reduce the scar area by anti-inflammation way after MI in rats (51).

Conclusions

A large number of studies have shown that the AT2 receptor plays a major role as a AT1 receptor antagonist, but other studies challenge this observation. Diverse expression and function of AT2R in different individuals, tissue, and pathological conditions may explain these contradictory results. ARB is widely used for patients with hypertension and other cardiovascular pathologies. It predominantly blocks the Ang II AT1R to achieve its clinical effect. Obviously, in the setting of AT1R blockage by ARB molecules, increasing amount of Ang II will combine with the AT2R, with incompletely understood effect on cardiovascular homeostasis. Therefore to understand the pharmacological effects of ARB, further studies are necessary to clarify the cardiovascular effects of the AT2R.

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