Angiotensin II and the hypertensive heart: a role for the AT2 receptor?
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Arterial hypertension is associated with complex structural and functional alterations of its target organs. Hypertension-induced left ventricular hypertrophy, the essential criterion for hypertensive heart disease [1], initially serves as an adaptive ventricular response to pressure overload, but it is also associated with an increased risk of heart failure [2]. In response to mechanical stress, the left ventricular myocardium undergoes structural remodelling involving cardiomyocyte hypertrophy and myocardial fibrosis [3]. Cardiomyocyte hypertrophy involves an increase in contractile and fetal protein content, which occurs when transcription of genes that encode for these cardiac proteins are activated [4]. Myocardial fibrosis is the result of exaggerated interstitial and perivascular deposition of collagen type I and III fibres, which is a consequence of the predominance of the synthesis over the degradation of collagen type I and III molecules [5]. There is evidence to suggest that these changes are involved in the progressive decline of cardiac function over time, which underlies the pathogenesis of heart failure in hypertensive heart disease [6,7]. It is now accepted that, in addition to the mechanical effects of pressure overload, a number of systemically and locally expressed factors have key roles in the process of myocardial remodelling associated with hypertension. One of these factors is angiotensin II.

Angiotensin II is a multifunctional hormone that not only influences the function of the heart through its short-term effects on systemic haemodynamics and blood volume, but also exerts long-term structural and functional effects through its direct actions on specific receptors present in cardiac cells. In humans, the AT1 receptor is expressed at relatively constant levels in the adult heart [8]. By contrast, the AT2 receptor, which is poorly expressed in the normal adult human heart, is upregulated in various pathological conditions associated with tissue remodelling, including hypertension, heart failure, postmyocardial infarction, ischemia and diabetes [8]. Depending on the species, angiotensin II receptors of both subtypes, AT1 and AT2, are equally expressed in cardiomyocytes [8,9]. Cardiac fibroblasts express only AT1 receptors under normal conditions, but can reactivate the AT2 receptor in pathological conditions, such as heart failure [8,9].

To the best of our present knowledge, extensive pharmacological evidence indicates that most of the known effects of angiotensin II in adult cardiac cells are attributable to the AT1 receptor. For example, the AT1 receptor mediates hypertrophic effects of angiotensin II in isolated cardiomyocytes via activation of several kinase-mediated signalling pathways, especially the protein kinase C pathway [10]. In vitro, angiotensin II, via the AT1 receptor, causes not only left ventricular hypertrophy independently of blood pressure, but also a shift to the fetal phenotype of the myocardium [11]. Angiotensin-converting enzyme inhibitors and AT1 receptor antagonists not only induce the regression, but also prevent the development of cardiac hypertrophy in hypertension [12]. On the other hand, stimulation of the AT1 receptor in cultured cardiac fibroblasts activates the mitogen-activated protein kinases and the JAK/STAT pathway, which induce expression of fibrosis-related proteins such as transforming growth factor β and fibrillar collagens as well as cell proliferation [13]. In addition, a number of experimental and clinical findings obtained in vivo suggest that the interactions of angiotensin II with the AT1 receptor may alter fibrillar collagen turnover in the hypertensive heart, resulting in the accumulation of collagen type I and III fibres [14].

Because less is known about the AT2 receptor, recent work has attempted to unravel the AT2-dependent effects in vitro using selective AT2 antagonists or agonists in isolated cardiac cells. Studies employing AT2 antagonists have shown antihypertrophic effects of this receptor in rat ventricular cardiomyocytes [15,16]. More recent studies have shown that angiotensin II-induced apoptosis in cultured rat cardiomyocytes is mediated through activation of both AT1 and AT2 receptors [17,18]. The available data suggest that the activation of the AT2 receptor leads to dephosphorylation of the anti-apoptotic protein Bcl-2 and upregulation of the pro-apoptotic protein Bax [19]. Studies...
performed in cultured cardiac fibroblasts have demonstrated that the AT2 receptor does not mediate the ability of angiotensin II to induce either collagen synthesis and secretion or cellular proliferation [20,21]. However, AT2 stimulation results in both activation of collagenase and inhibition of tissue inhibitor of metalloproteinase-1 [22,23], which in turn facilitates the degradation of collagen molecules.

Most of the information on the cardiac effects of the AT2 receptor in vivo have been obtained in genetically modified mice that either lack the gene coding for AT2 or overexpress it. Early evidence showed that aortic binding induced marked left ventricular hypertrophy in wild-type mice but not in mice lacking the AT2 receptor (AT2− mice) [24]. The same group reported that angiotensin II-induced hypertension was associated with hypertrophy, fibrosis and impaired diastolic relaxation in wild-type mice, but not in AT2− mice [25]. Recently, it was reported that neither aortic coarctation, nor chronic infusion of a pressor dose of angiotensin II, resulted in left ventricular hypertrophy in transgenic mice overexpressing the AT2 receptor in a cardiacspecific manner [26]. On the other hand, it was found that aortic binding resulted in similar hypertrophy but increased perivascular fibrosis in AT2− mice compared to wild-type mice [27]. Furthermore, in conditions of angiotensin II-induced hypertension, transgenic mice overexpressing the AT2 receptor developed similar hypertrophy but lower perivascular fibrosis than wild-type mice [28]. Thus, whereas the findings from the first two studies suggest that the AT2 receptor plays a role in myocardial injury associated with hypertension, the third study does not support a role for this receptor in conditions of pressure overload of the heart, and the findings provided by the last two studies indicate a protective role of the AT2 receptor against the detrimental cardiac effects of experimental hypertension. These conflicting data are most probably due to the different genetic models and/or experimental protocols employed.

In this issue of the journal, Gross et al. [29] describe how chronically Nω-nitro-L-arginine methyl ester (L-NAME) treated AT2− mice showed higher left ventricular hypertrophy and fibrosis, and lower left ventricular contractility than L-NAME treated wild-type mice, despite a similar increase in blood pressure induced by L-NAME in the two strains. No changes in diastolic function were observed in either group of treated animals. Although these findings add further support to the notion of the protective role of the AT2 receptor, some aspects deserve to be considered. First, as previously shown in other tissues in AT2− mice [30–33], Gross et al. [29] found that the AT1 receptor was upregulated in the heart of AT2− mice. If AT1 and AT2 receptors exert antagonistic action on myocardial biology, especially in response to injury, then the relative expression of these receptors and their ratios may be important in determining myocardial structure and function. Thus, the effects observed by Gross et al. [29] in AT2− mice may be related to the lack of AT1 receptors and/or the excess of AT1 receptors. Second, it has been demonstrated that nitric oxide (NO)-dependent mechanisms may be critically involved in the cardiac protective actions associated with the stimulation of the AT2 receptor in conditions of either haemodynamic [28] or ischaemic [34,35] injury of the heart. Because the NO system was abolished in the study by Gross et al. [29], some of the cardiac effects observed in L-NAME-treated, wild-type mice may also reflect the lack of function of the AT2 receptor in these animals. Finally, although some data reported by Gross et al. [29] would suggest that the AT1 receptor may protect left ventricular contractility in the hypertensive heart, it is unclear what the true influence of this receptor on cardiac function is. Studies performed in AT2− mice suggest that this receptor may improve left ventricular function at baseline and preserve function after post-myocardial infarction remodelling [36,37]. By contrast, it has been reported that ventricular overexpression of AT2 receptors promotes the development of dilated cardiomyopathy and heart failure in transgenic mice [38]. On the other hand, AT2− mice displayed no major changes in left ventricular function at baseline or in response to deoxycorticosterone acetate-salt-induced hypertension compared to wild-type mice [39].

Although much work is still necessary to ascertain the contribution of the AT2 receptor to the pathophysiology of cardiac diseases, namely hypertensive heart disease, there are two aspects that might be of potential clinical relevance. On the one hand, recent studies [40,41] have shown that the +1675 G/A polymorphism of the AT2 receptor gene is associated with left ventricular hypertrophy in hypertensive patients. The influence of the G/A genotype on the left ventricle was independent of a number of confounding factors, including haemodynamic load and plasma angiotensin II. The +1675 G/A polymorphism was suggested to be a functional variant in that it involves a lariat branch-point motif in intron 1, leading to a diminished AT2 receptor splice efficiency [42]. Furthermore, this sequence region is adjacent to an intron fragment that was shown to direct AT2 gene transcription in the absence of the AT2 receptor gene [43]. It is conceivable that the polymorphism is transcriptionally functional in that the A allele might be associated with some degree of loss-of-function, leading to decreased AT2 gene transcription and, accordingly, a decreased number of AT2 receptors. The other possible scenario involves the putative branchpoint in intron 1, where the presence of the A allele might lead to a different and perhaps less functional AT2 receptor transcript with respect to receptor transcription.
On the other hand, it has been well established that AT₁ receptor antagonists constitute a safe and effective group of antihypertensive drugs with a clear indication in patients with hypertensive heart disease [12]. When the AT₁ receptor is blocked, renin and angiotensins increase [44], and therefore increased angiotensin II may act preferably on the AT₂ receptor. In accordance with this, it has been proposed that the increased stimulation of the AT₂ receptor that occurs in the presence of AT₁ blockade contributes to the benefits of AT₁ receptor antagonists [45]. In support of this view are the findings that the cardioprotective effects and improved cardiac function afforded by AT₁ receptor antagonists in experimental models of heart failure can be abrogated by an AT₂ antagonist [46] or by the disruption of the AT₂ gene [47]. However, the data reviewed here indicate that the cardiac effects of AT₂ are context dependent and that the long-term cardiac consequences of AT₂ stimulation might be less beneficial than was previously assumed and could even be harmful in some circumstances [48]. For example, the ability of angiotensin II to induce apoptosis through stimulation of the AT₂ receptor might be involved in cardiomyocyte apoptosis present in patients with hypertensive heart disease treated with losartan [49]. Interestingly, apoptosis may be a contributing cause of the loss and functional abnormalities of cardiomyocytes that participate in the transition from compensated left ventricular hypertrophy to heart failure in arterial hypertension [50]. The concept that increased stimulation of the AT₂ receptor may have negative as well as positive effects provides a possible explanation for AT₁ receptor antagonists failing to live up to the high cardiac expectations, in all large-scale randomized clinical trials performed to date, that they would prove to be superior to angiotensin-converting enzyme inhibitors in the context of chronic heart failure.

References

hypertrophy is associated with decreased eNOS expression in angiotensin II receptor-deficient mice. Hypertension 2003; 42:1177–1182.


