Review Article

Genetically Modified Mouse Models Used for Studying the Role of the \( \text{AT}_2 \) Receptor in Cardiac Hypertrophy and Heart Failure

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The actions of Angiotensin II have been implicated in many cardiovascular conditions. It is widely accepted that the cardiovascular effects of Angiotensin II are mediated by different subtypes of receptors: \( \text{AT}_1 \) and \( \text{AT}_2 \). These membrane-bound receptors share a part of their nucleic acid but seem to have different distribution and pathophysiological actions. \( \text{AT}_1 \) mediates most of the Angiotensin II actions since it is ubiquitously expressed in the cardiovascular system of the normal adult. Moreover \( \text{AT}_2 \) is highly expressed in the developing fetus but its expression in the cardiovascular system is low and declines after birth. However the expression of \( \text{AT}_2 \) appears to be modulated by pathological states such as hypertension, myocardial infarction or any pathology associated to tissue remodeling or inflammation. The specific role of this receptor is still unclear and different studies involving in vivo and in vitro experiments have shown conflicting data. It is essential to clarify the role of the \( \text{AT}_2 \) receptor in the different pathological states as it is a potential site for an effective therapeutic regimen that targets the Angiotensin II system. We will review the different genetically modified mouse models used to study the \( \text{AT}_2 \) receptor and its association with cardiac hypertrophy and heart failure.

1. Introduction

Angiotensin II (Ang II) plays a pivotal role in the regulation of the cardiovascular system [1, 2]. It is known that the effects of Ang II are mediated by several subtypes of Ang II receptors; these receptor subtypes differ from each other on their pharmacological and biochemical properties. Up until now, the subtypes that have been identified are the Type 1 (\( \text{AT}_1 \)) and the Type 2 (\( \text{AT}_2 \)) present in humans, and \( \text{AT}_{1\alpha} \) and \( \text{AT}_{1\beta} \) present in rodents [2]. Both of these receptors, \( \text{AT}_1 \) and \( \text{AT}_2 \), belong to the seven-transmembrane domain superfamily of receptors, and they share 34% of their nucleic acid sequence. The \( \text{AT}_1 \) receptor is widely distributed in adult tissues (blood vessels, kidney, adrenal gland, heart liver, and brain). The \( \text{AT}_2 \) receptor is ubiquitously expressed in fetal tissues but the expression of the \( \text{AT}_2 \) receptor declines rapidly after birth with very low abundance in ventricular myocytes and vascular endothelium and absence in fibroblasts [3, 4]. Most of the distinct effects of Ang II on vasomotor tone, contractility, and myocardial growth are mediated by \( \text{AT}_1 \) receptors [5, 6] but various studies from the past two decades have demonstrated involvement of the \( \text{AT}_2 \) receptor in some important actions of Ang II in the heart. However, the specific role of the \( \text{AT}_2 \) receptor still remains unclear [5–7] as there have been contradictory results in the different studies performed.

Accumulating evidence suggests that the \( \text{AT}_2 \) receptor may act as an \( \text{AT}_1 \) receptor antagonist, as its activation has been associated with opposite cellular functions of \( \text{AT}_1 \), such as antigrowth, antihypertrophic, and proapoptotic effects [8, 9]. If these receptors exert opposing actions in the heart, their ratio of expression under different cardiac pathologies may determine myocardial function and structure. Experiments using hypertrophic hearts have demonstrated that the cardiac expression of \( \text{AT}_1 \) and \( \text{AT}_2 \) receptors changes during the process of cardiac hypertrophy allowing the heart to respond differently to Ang II. Studies have shown that the pathological hypertrophy and failure of human hearts...
are associated with a decrease of AT₁ and an increase of AT₂ receptor expression, that is, an increase of AT₂-to-AT₁ ratio [10, 11]. In patients treated with AT₁ antagonists, circulating Ang II levels are increased and may preferentially bind to AT₂ receptors inducing several effects that still remain controversial.

In order to develop a safer and more effective therapeutic regimen by targeting the Ang II system, it becomes essential to clarify the role of the AT₂ receptor in the development of cardiac hypertrophy and failure. With the objective of clarifying the specific actions of the AT₂ receptor in cardiac hypertrophy and heart failure, different approaches have been developed including in vivo and in vitro experiments. However, results from these studies have been inconsistent. This paper will review the different genetically modified mouse models used to study the AT₂ receptor and its association with cardiac hypertrophy and heart failure.

2. Angiotensin II Type 2 Receptor Mouse Models

Mice had been extensively used as a model for cardiovascular research; not only due to their short gestation period but also because there is significant preservation of the molecular pathways that control cardiovascular development and function between mice and humans [12]. Different approaches to genetic modification in the mouse such as gene deletion or overexpression have been described [13]. These animal models have become invaluable tools to study cardiovascular genetics, developmental biology, and physiology in normal or pathologic hearts [12, 13].

Compared to in vitro cardiomyocyte culture and pharmacological intervention, genetically modified mouse models have provided a novel and powerful method to study the physiological function of the AT₂ receptor. First, this technique allows us to study the function of the gene of interest in a physiological setting; second, it reduces the off-target effects of pharmacological inhibitors. It was hoped that genetic deletion or overexpression of the receptor would provide a much clearer picture of AT₂ in cardiac hypertrophy and failure. Currently, there are two AT₂ overexpression and two AT₂ knockout mouse models that have been generated [14–17]. Unexpectedly, the results from these mouse models are contradictory and have raised more questions in the field.

### 2.1. Transgenic Mice with Cardiomyocyte-Specific Overexpression of AT₂

Two transgenic (TG) mouse models with cardiomyocyte-specific AT₂ overexpression have been generated [14, 15]. In the first model, the AT₂ receptor was overexpressed in both atria and ventricles, using the α-myosin heavy chain promoter in C57BL/6 mice [15]. Studies using this transgenic mouse model showed that the TG mice did not present any abnormality in myocardial development or phenotype when compared to nontransgenic (NTG) mice [15, 18]. Under baseline condition, the heart weight (HW) to body weight (BW) ratio was similar between TG and NTG mice. However, TG mice showed a higher end-diastolic wall thickness [18, 19]. Heart rate was similar between TG and NTG, while ejection fraction (EF%) was higher in TG mice [18]. Aortic stenosis (AS) in adult mice or with chronic Ang II infusion significantly increased HW/BW in mice compared to control mice; but HW/BW was not different between TG and NTG mice [19]. Ang II infusion in mice reduced HR in TG mice, but did not increase apoptosis [18]. Myocardial infarction (MI) increased left ventricular mass index (LVMI) in mice, with no difference between TG and NTG mice. LV wall thickness and EF%, however, maintained higher in TG versus NTG mice after MI [18] (Table 1).

Our laboratory has generated a mouse model with ventricular myocyte-specific overexpression of the AT₂ receptor using α-myosin heavy chain 2v (MLC2v) promoter in FVB/n mice [14]. We generated four lines of mice with different copy number of the AT₂ gene [14]. This allowed us to study the dose-response of AT₂ overexpression. We have studied two lines of AT₂ transgenic mice with relatively high (AT₂-high TG) and low (AT₂-low TG) expression of AT₂. We found that under baseline condition, the left ventricular to body weight ratio (LV/BW) was increased in AT₂-high TG mice; this was accompanied by a decrease of LV wall thickness, an increase of cardiomoyocyte area and length, and an increase of interstitial spaces and the deposition of fibrillar collagen in AT₂-high TG mice [14]. LV systolic function, as assessed by echocardiography and hemodynamic measurements, was significantly depressed in AT₂-high TG [14]. The contractile function of cardiomyocytes isolated from AT₂-high TG mice was significantly decreased under baseline and in response to Ang II [20]. These results suggest that excessive AT₂ overexpression can induce pathological cardiac remodeling and failure. Mice with low AT₂ overexpression (AT₂-low TG), however, did not demonstrate a significant change in cardiac morphology and function at baseline [14]. We further tested whether AT₂ overexpression would modify cardiac remodeling in aortic stenosis- (AS-) induced hypertrophy using AT₂-low TG mice [21]. Our results showed that 70 days after AS, LV/BW and LV wall thickness were increased in AS mice, with no difference between AT₂-low TG mice and NTG mice. However, LV myocyte diameter was smaller and the percentage of LV collagen was lower in AT₂-low TG versus NTG mice. LV systolic pressure and peak dP/dt± were lower in AT₂-low TG versus NTG mice, with no decrease in wall thickness. LV end diastolic pressure was lower in AT₂-low TG versus NTG mice [21]. These results suggest that lower level AT₂ overexpression did not accelerate cardiac hypertrophy and failure in AS mice; it is likely that the diastolic compliance was improved in AT₂-low TG mice (Table 1).

These two transgenic mouse models are different in several aspects: (1) the strain of mice (C57BL/6 versus FVB/n), (2) the AT₂ overexpression site (atria + ventricles versus ventricles), and (3) the overexpression level of AT₂. The site of AT₂ overexpression may be the cause of HR changes in mice using α-MHC promoter [15], which was not observed in mice using MLC2v promoter [14]. Despite the difference of the models, the results from these studies demonstrate that the expression level of AT₂ is a key determinant of outcome. Excessive AT₂ overexpression can lead to cardiac failure, while lower AT₂ overexpression may improve cardiac performance under stress.
2.2. AT$_2$ Knockout Mouse Models. Two AT$_2$ knockout (KO) mouse models were generated at the same time by two independent research groups [16, 17]. Both models were generated by targeted disruption of the AT$_2$ gene on the X chromosome [16, 17]. The results from these two models, however, are different. The first model was generated in C57BL/6 mice [16]. Under baseline condition, blood pressure (BP) was higher in KO mice. LVW/BW, wall thickness and LV mass (LVM) were lower in KO versus wild-type (WT) mice [16, 22, 23]. Cardiac function did not change in KO versus WT [22]. The second striking result from this model is that AT$_2$ knockout prevented the cardiac hypertrophic response to both aortic stenosis (AS) and chronic Ang II infusion in mice [22, 23]. Cardiac function was either similar between KO and WT (AS) or improved in KO versus WT (Ang II infusion) mice [22, 23]. These results suggest that AT$_2$ is essential for the development of cardiac hypertrophy and dysfunction (Table 1).

The second AT$_2$ KO mouse model was generated in FVB/n mice [17]. Unlike the first model, under baseline condition, BP was not different between KO and WT and no changes in cardiac morphology were observed [24]. Aortic stenosis resulted in a similar increase of HW/BW in KO versus WT mice, while the perivascular fibrosis was higher in KO mice [24]. Acute myocardial infarction resulted in higher mortality rate, higher LVW/BW, lung/BW, ratio and decreased EF% in KO versus WT mice [25] (Table 1). These results suggest that AT$_2$ has antihypertrophic remodeling effects and may be important for maintaining cardiac function under certain stress.

The contradictory results from these two models may be caused by the different mouse strains and the different disease models used. However, they also suggest that traditional gene deletion approach in mice may lead to the activation of compensatory mechanisms and ultimately different phenotypes.

3. Limitations of the Existing Mouse Models

The existing AT$_2$ mouse models have several limitations: (1) the models cannot recapitulate the AT$_2$ receptor expression patterns during pathological hypertrophy and failure. Studies have shown that AT$_2$ receptor expression is high in the fetus [3], significantly decreased in adult hearts, and increased again in diseased hearts in humans [7]. While AT$_2$ receptors are chronically overexpressed or disrupted in these models; (2) the expression level of AT$_2$ receptors in transgenic mouse hearts may not represent the increase of AT$_2$ receptors in a diseased heart. Studies in transgenic mice clearly showed a dose-relationship between AT$_2$ overexpression and cardiac remodeling and function. Further experiments by using mice with cardiac AT$_2$ receptors expression similar to that in diseased hearts are needed; (3) the cell type of AT$_2$ receptor overexpression may be not accurate. Studies have shown that fibroblasts are the major cell type that expresses AT$_2$ receptors in diseased human hearts [26]. In current mouse models the AT$_2$ receptor is overexpressed in cardiomyocytes; (4) chronically manipulation of AT$_2$ receptors expression may activate compensatory mechanisms, which may lead to phenotypes that are not related to AT$_2$ receptors.

3.1. In Vitro Studies. In order to understand better the role of AT$_2$ receptors in the heart and in cardiac pathology, it is important to review what in vitro studies have shown and how they differ from the mouse models mentioned above. Studies using cultured rat neonatal cardiomyocytes, fibroblasts, and coronary endothelial cells have shown that the stimulation of the AT$_2$ receptor inhibits cell growth and proliferation and opposes the effects of the AT$_1$ receptor [27, 28]. Nakajima C. et al. used AT$_2$ receptor expression vectors to evaluate the growth of cultured aortic vascular smooth muscle cells (VSMC) with overexpression of these receptors versus controls. In this study, VSMCs with transfection of the AT$_2$ receptor presented a decrease of 70% in neointimal area when compared to controls, suggesting that the AT$_2$ receptors have an inhibitory effect of neointimal growth. Moreover, this effect was blocked with PD123319, an AT$_2$ receptor antagonist [29].

On the other hand, a direct prohypertrophic action of AT$_2$ receptors on cardiomyocytes was demonstrated by D’Amore et al. when using adenoviruses encoding AT$_1$ and AT$_2$ to coexpress these receptors in isolated cardiomyocytes [30]. Overexpression of the AT$_2$ receptor on cardiomyocytes using adenoviruses provoked an increase in the basal hypertrophy of these cells. This was unaffected by Ang II or AT$_2$ receptor ligands such as PD123319 or CGP42112A. The major outcome of this study was the lack of evidence to demonstrate that the AT$_2$ receptor opposes the actions of the AT$_1$ receptor, a widely proposed view. When the expression of the AT$_2$ receptor was increased, the Ang II-mediated hypertrophy through the AT$_1$ receptor was not inhibited; moreover, the AT$_2$ receptor-mediated enhanced basal hypertrophy was unchanged and it was added to that of the AT$_1$ receptor. These findings suggest that the AT$_1$ and AT$_2$ receptor might use different pathways.

Results from in vitro cell culture have provided invaluable information regarding the role of the AT$_2$ receptor in mediating the Ang II signaling and the interaction of the AT$_1$ and AT$_2$ receptor in specific cell types. Different studies involving the AT$_2$ receptors showed that there is marked tissue heterogeneity, likely a reflection of the balance of AT$_1$/AT$_2$ receptor expression [31]. The various growth effects of Ang II seen in the in vitro studies were determined by the type of AT$_2$ receptor expressed in the cultured cell. For example, the AT$_2$ receptors are constitutively expressed in cultured endothelial cells but not in cultured vascular smooth muscle cells (VSMC); consequently, the AT$_2$ receptor antiproliferative effects will counteract the AT$_1$ receptor growth promoting effects in endothelial cells but not in vascular smooth muscle cells [27, 29]. This might explain why the results of the different in vitro studies are not 100% consistent and why these results differ from in vivo experiments. Furthermore, cell culture may not reflect the complex cross-talk among different cell types in the heart in vivo. In regards to the studies of the diseased heart even
### Table 1: Cardiac phenotype and function in mice with AT2 overexpression (TG) or knock out (KO).

| Mouse model | Strain | Baseline | Disease state | References |
|-------------|--------|----------|---------------|------------|
| AT2 TG mice (cardiomyocyte-specific, α-MHC) | C57BL/6 | ↓HW/BW, ↓PW, ↓EF% | AS: ↓HW/BW, ↓PW, ↓EF% | [15, 18, 19] |
| AT2 TG mice (ventricular myocyte-specific, MLC-2v) | FVB/n | ↓LVW/BW, ↓wall thickness, ↓Interstitial collagen, ↓myocyte area and length | ↓apoptosis | ↓LVW/BW, ↓wall thickness, ↓myocyte diameter | [14] |
| AT2 KO mice | C57BL/6 | ↓BP, ↓HR, ↓LVW/BW, ↓LVMl | ↓BP, ↓Interstitial collagen, ↓contractile function | ↓BP, ↓Interstitial collagen, ↓diastolic function | [16, 22, 23] |
| AT2 KO mice | FVB/n | ↓BP, ↓Cardiac morphology | ↓BP, ↓Heart rate, ↓Interstitial collagen, ↓Contractile function | ↓BP, ↓Heart rate, ↓Interstitial collagen, ↓Contractile function | [17, 24, 25] |

HW: heart weight; LVW: left ventricular weight; BP: blood pressure; HR: heart rate; LVMl: left ventricular mass index; PW: posterior wall thickness; EF: ejection fraction; AS: aortic stenosis; Ang II: Ang II infusion; MI: myocardial infarction.

though it is well known that AT2 receptors are upregulated in cardiac fibroblasts in the presence of cardiac pathology [26, 32, 33], it is not known whether the ratio of AT1/AT2 by overexpression of these receptors in cell cultures represented that in a hypertrophied/failing heart.

### 4. Conclusions

Transgenic mouse models with specific AT2 overexpression or disruption have provided new information on this receptor. However, these results need to be interpreted with caution. New transgenic mouse models that conditionally overexpress or disrupt AT2 in specific cell types in addition to cardiomyocytes in the heart may be used for more precisely studying the pathophysiological role of AT2 receptors.

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