Angiotensin II type-1 receptor activation in the adult heart causes blood pressure-independent hypertrophy and cardiac dysfunction

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Aims Sustained hypertension leads to cardiac hypertrophy that can progress, through pathological remodelling, to heart failure. Abnormality of the renin–angiotensin system (RAS) has been strongly implicated in this process. Although hypertrophy in human is an established risk factor independent of blood pressure (BP), separation of remodelling in response to local cues within the differentiated myocardium from that related to pressure overload is unresolved. This study aimed to clarify the role of local RAS activity, specifically in the adult heart, in modulating cardiac hypertrophy and pathological remodelling.

Methods and results Transgenic mice with inducible cardiomyocyte-specific expression of a wild-type or N111G mutant form of the human angiotensin II (Ang II) type-1 receptor (hAT1R) were generated. The wild-type receptor is primarily stimulated by Ang II. In contrast, the N111G receptor can also be fully stimulated by the Ang II derivative, Ang IV, at levels that do not stimulate the wild-type receptor. The unique properties of these models were used to investigate the myocardial growth, remodelling and functional responses to hAT1R stimulation, specifically in adult cardiomyocytes, under normal conditions and following Ang IV infusion. Low-level expression of wild-type or N111G hAT1R at the cardiomyocyte membrane, from the onset of adolescence, induced enhanced myocyte growth and associated cardiac hypertrophy in the adult. This was not associated with change in resting BP or heart rate, measured by longitudinal telemetric analysis, and did not progress to pathological remodelling or heart failure. However, selective activation of cardiomyocyte-specific N111G receptors by Ang IV peptide infusion induced adverse ventricular remodelling within 4 weeks. This was characterized by increased interstitial fibrosis, dilatation of the left ventricle, and impaired cardiac function.

Conclusion Low-level local AT1R activity in differentiated myocardium causes compensated cardiac hypertrophy, that is, increased myocardial mass but with the retention of normal function, whereas short-term increased stimulation induces cardiac dysfunction with dilatation, reduced ejection fraction, and increased fibrosis in the absence of change in systemic BP.

1. Introduction

Although heart failure is often preceded by hypertension-induced ventricular hypertrophy, hypertrophy is a risk factor in its own right.1–5 As hypertrophy and hypertension are intrinsically linked, challenging questions remain regarding their relative contribution to the disorder. The development of the mammalian heart is a highly regulated process, involving a phase of rapid proliferation as the distinct chambers and outflow tracts are formed.6 Post-natally, the increase in myocyte number slows as the cells undergo a transition from proliferation to growth and terminal differentiation (Figure 1A). Although the increase in cardiac mass slows dramatically in adulthood, certain stimuli, including exercise and haemodynamic overload, can stimulate further growth.7 Failure to inhibit growth may initiate pathological remodelling with the reactivation of genes whose expression is normally restricted to the developing heart.8 The triggers that promote switching from the normal state through hypertrophy to pathological remodelling are not understood.

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Angiotensin II (Ang II), a key component of the renin–angiotensin system (RAS), acts to modulate arterial pressure, regulate blood volume, and promote growth and proliferation through the activation of widespread signalling mechanisms. This occurs primarily through its type-1 receptor (AT1R). However, RAS activity has been implicated in heart failure beyond its influence on blood pressure (BP), with the evidence that selective blockade reduces left ventricular hypertrophy. In addition to the system-wide activation by Ang II, the AT1R can be stimulated locally by mechanical stretch, and could therefore play a key role in promoting localized growth, for example, in response to exercise.

Given the ubiquitous nature of the RAS, separating the effects of systemic and localized activity has been difficult. Angiotensin II (Ang II), a key component of the renin–angiotensin system (RAS), acts to modulate arterial pressure, regulate blood volume, and promote growth and proliferation through the activation of widespread signalling mechanisms. This occurs primarily through its type-1 receptor (AT1R). However, RAS activity has been implicated in heart failure beyond its influence on blood pressure (BP), with the evidence that selective blockade reduces left ventricular hypertrophy. In addition to the system-wide activation by Ang II, the AT1R can be stimulated locally by mechanical stretch, and could therefore play a key role in promoting localized growth, for example, in response to exercise.

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Figure 1 Transgenic mice with conditional myocyte-specific hAT1R expression. (A) Temporo-spatial pattern of αMHC promoter activity. Initial expression occurs in the proliferating/differentiating heart tube, then embryonic atria, and subsequently post-natal atria and ventricle. Myocyte proliferation/differentiation potential is downregulated within a month of post-natal development. Transgene activation (arrow) in this study is restricted to mature myocytes to avoid complications from an embryonic developmental phenotype. (B) The transgene contains the human wild-type (or N111G mutant) hAT1R and LacZ reporter flanking tetracycline response element (TRE) minimal CMV promoters. After mating with αMHC-tTA transgenic mice binding of tTA to TRE drives transgene expression specifically in myocytes. Transgenic founders were mated with C57/BL6 mice and progeny analysed by Southern blotting to determine copy number and methylation status, using a radiolabelled hAT1R probe. Three lines, hAT1R-wt1, hAT1R-mut1, and hAT1R-mut2, were used in subsequent analysis. wt, wild-type hAT1R; mut, N111G mutant hAT1R.
A number of murine models, designed to over-express AT1Rs specifically within the heart, have been developed to address this.13–16 However, the interpretation has been confounded by the fact that the expression is induced during the embryonic and proliferative early post-natal stages of myocardial development (Figure 1A). In human, pathological remodelling takes place in later years, after the heart has developed. Here we describe a new model that separates the effects of AT1R activation in the adult heart from effects in development, as well as isolating the local from the systemic effects.

We found that moderate AT1R upregulation in adult cardiomyocytes induced hypertrophy similar in magnitude to that observed in human, without altering BP, whereas further selective stimulation of the cardiomyocyte-specific receptors promoted pathological remodelling.

2. Methods

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Approval for the work was granted by the University of Leeds Ethical Review Committee. This section summarizes key methods in abbreviated form. A full description of all methods is found in the Supplementary material online.

2.1 Transgenic mice and initial characterization

DNA was injected into fertilized CBA/C57BL6 eggs as described previously.17,18 Transgenic founders were identified by PCR and Southern blot. Selected lines were backcrossed for four generations onto C57/BL6 and mated with αMHC-tTA transgenic mice to activate myocyte-specific transgene expression.19 The expression was repressed during development by the addition of doxycycline (dox) to drinking water. Northern/Southern blotting, copy number and methylation analyses were performed as described.20–22

2.2 Cardiac weight index

After recording whole-body weight, the heart was removed and washed. Atria and the lung were assayed for LacZ. Ventricles were cleaned of blood, blotted, and weighed. Ventricle-to-body weight ratio (mg/g) was recorded as cardiac weight index.

2.3 Radioligand binding

Human Ang II type-1 receptor (hAT1R) expression level and binding characteristics were determined in heart membranes at 12 months, by incubating with \[^{125}\text{I}[^{Sar}[^{1},[^{Ile}[^{3}]]]\text{Ang II for saturation, or}^\text{125I-[^Sar}[^{1},[^{Ile}[^{3}]]}\text{Ang II in the presence of Ang IV for competition experiments.}

2.4 Histology and expression analyses

Frozen sections were stained with Rhodamine-WGA to identify cell membranes and fibrosis, Hoechst-33258 for cell nuclei, and Alexa Fluor conjugated-anti-cleaved caspase-3 for the analysis of apoptosis. Fluorescence imaging was performed using a Zeiss axiovert-200 confocal laser scanning microscope. LacZ activity was assayed as described previously.21 ERK phosphorylation was determined by immunoblotting.22

2.5 Cardiovascular variables

Arterial BP (mean, systolic, and diastolic) and heart rate (HR) were measured by radiotelemetry. The probe catheter was advanced into the ascending aorta via the left carotid artery. Twenty-four-hour recordings were obtained by sampling for 2 min every 15 min. For Millar catheter analysis, a pressure–volume catheter was inserted into the left ventricle via the right carotid artery.

2.6 Angiotensin IV infusion

Ang IV was delivered continuously at 5 µg/kg/min for 4 weeks via subcutaneously implanted miniosmotic pump.

2.7 Statistical analysis

Data are expressed as mean ± SEM. Unless otherwise stated, data samples were analysed by unpaired t-test using GraphPad Prism v5.01. Ligand-binding data were analysed by non-linear regression. Competition curves were fitted to three-site models, and F-test was used to determine the most appropriate model.

3. Results

3.1 Transgenic hAT1R-mut and -wt mice

A number of AT1R mutations have been identified that induce a constitutively active state.24,25 The N111G mutant exhibits basal activity, which is 20% of the fully activated wild-type receptor.26,27 Thus, this form of the receptor will partially induce intracellular signalling even in the absence of Ang II, whereas in the presence of Ang II it is fully active. Unlike the wild-type receptor, the N111G mutant can be activated by the Ang II byproduct, Ang IV. The wild-type human and endogenous mouse receptors exhibit almost 10 000-fold lower affinity for Ang IV than the human N111G mutant receptor.28 These significant differences allow the use of the human N111G mutant and Ang IV to isolate the activation of transgenic receptors from wild-type human or endogenous mouse receptors. Furthermore, in the model described here, the expression of transgenic human receptors is under the control of an inducible promoter through which the expression can be limited to the myocardium following activation at any time in development.

We generated 10 founder mice with stable integrations of human wild-type or N111G mutant receptor transgenes (Figure 1B). By mating with transgenic mice expressing the tetracycline transactivator molecule, tTA, in cardiomyocytes, the local activation of human receptor and LacZ reporter gene expression is achieved.19 Thus, in double-transgenic progeny, temporal activation is controlled by the addition of dox, which binds the tTA molecule and holds it in an inactive state.

Southern blot analysis showed that transgene copy number ranged from 2 to over 30 in progeny from each of the 10 lines. However, the promoter regions of many lines were found to be highly methylated (Figure 1B), suggesting that these transgenes were less likely to be tTA-activatable. Of the three lines that were unmethylated, one contained two copies of the human wild-type receptor transgene (hAT1R-wt1), whereas the other two contained three and five copies of the human N111G mutant transgene (hAT1R-mut1 and hAT1R-mut2, respectively).

3.2 Transgene activation in cardiomyocytes

Mice from each line were mated with αMHC-tTA mice,19,29 and progeny that inherited both transgenes were tested for gene activation. As expected, lines with highly methylated promoters only showed LacZ activation in <5% of
individual cardiomyocytes (not shown), and were not ana-
lysed further. However, lines hAT1R-wt1, hAT1R-mut1, and
hAT1R-mut2 showed strong cardiomyocyte-specific LacZ
activation in both neonatal and adult hearts (Figure 2A).
Interestingly all three lines also showed expression in the
pulmonary veins (Figure 2B), but not in other blood vessels
or tissues. Northern blot analysis of receptor expression in
these lines confirmed bi-directional activity of the transgene
and the suitability of using LacZ to report on cell-type speci-
ficity of expression (Figure 2C). When adults were given dox,
however, the receptor expression was repressed (Figure 2C,
lane 4). In addition, where matings were set up in the
presence of dox, double-transgenic progeny showed no
evidence of transgene activation until dox was removed
(not shown). Hereafter, animals that contain both trans-
genes in an active state are referred to as positive (+). Controls (−) include animals that contain either none or
only one of the transgenes.

Receptor protein expression was quantified in membranes
from whole hearts by measuring saturation-binding
isotherms, using 125I-[Sar1,Ile8]-Ang II. All transgenic lines
demonstrated significantly increased receptor levels, with
hAT1R-wt1+ hearts expressing at ~16-fold, hAT1R-mut1+ hearts at five-fold, and hAT1R-mut2+ hearts at 2.5-fold
above endogenous levels observed in controls (−),
(Figure 2D). Competition-binding experiments examined the
ability of Ang IV to compete with 0.1 nM 125I-[Sar1,Ile8]-Ang II (Figure 2E). Results for hAT1R-wt1+ mice suggested a
single low-affinity-binding site with an IC50 value of 23.6 ±
7.9 μM. In contrast, results for hAT1R-mut1+ mice suggested
a two-site model, with IC50 values of 2.5 ± 0.5 nM and
26.5 ± 14.2 μM for high (majority) and low (minority)
affinity-binding sites, respectively. This is consistent with
the superimposition of the 10 000-fold greater affinity of
the N111G mutant over the binding characteristics of the
endogenous receptor. As seen in other recent studies, there
was no evidence of lethality caused by upregulated
receptor activity at levels up to 16-fold within an 18 month
assessment period.

3.3 Low-level constitutive receptor activity
in adult cardiomyocytes induces hypertrophy

To determine whether inducing transgenic receptor expression
in adulthood causes cardiac hypertrophy, mice were weaned
off dox at 4 weeks after birth, leading to full activation
in the differentiated heart by 8 weeks (Figure 1A). Ven-tricle-to-body weight (CWI) measurements of 12-month-old

Figure 2 After mating hAT1R+ with αMHC-tTA mice, double-transgenic progeny show LacZ expression (blue) in cardiomyocytes (A) and pulmonary veins (B). hAT1R-mut1+ panels show adult heart and cross-section through pulmonary vein; hAT1R-mut2+ and hAT1R-wt1+ panels show neonatal heart and lung. (C) Northern blot analysis showing hAT1R expression in young adult double-transgenic mice. Progeny inheriting a single-transgene do not express receptors (lanes 1 and 2), those inheriting both do express (lanes 3, 5, and 6). Addition of doxycycline (dox) represses transgene expression (lane 4). (D) AT1R binding to radiolabelled 125I-[Sar1,Ile8] Ang II in heart membrane preparations: Bmax for control, hAT1R-wt1+, -mut1+, and -mut2+ was 13.2 ± 1.1, 203.8 ± 58.3
(16-fold), 61.2 ± 11.8 (5-fold), 33.9 ± 10.7 (2.5-fold) fmol/mg protein, respectively (n = 3 each). (E) N111G mutant receptors (black squares) exhibit ~10 000-fold greater affinity for Ang IV than wild-type receptors (black triangles), providing a concentration differential through which mutant receptors can be selectively activated.
males demonstrated a significant degree of hypertrophy in response to both wild-type and N111G receptor overexpression (Figure 3A and B). Hypertrophy was greater in hAT1R-mut1+ males than in hAT1R-wt1+ males, even though the mutant receptor was expressed at lower levels. Hypertrophy was less significant in hAT1R-mut+ females and completely absent in hAT1R-wt+ females (Figure 3C). It is worth noting that control females from all lines had a greater CWI than control males. These data are consistent with the constitutively active nature of the mutant receptor.

Figure 3 Activating hAT1R expression in mature myocytes causes ventricular hypertrophy. (A) Cardiac weight index at 12 months, where transgene expression was doxycycline-repressed until 4 weeks after birth, is significantly increased in males expressing transgenic receptors (hAT1R-mut1: 3.94 ± 0.30(−)), hAT1R-mut2: 3.88 ± 0.16(−)), hAT1R-wt1: 4.02 ± 0.21(−), 4.84 ± 0.25(+)). (B) LacZ-stained hearts from 12-month-old males show that those expressing transgenic receptors (blue) have hypertrophic left and right ventricles, but no overt indication of pathological remodelling. (C) The observed tendency towards hypertrophy in hAT1R-mut1+ females (4.41 ± 0.23(−), 5.23 ± 0.39(+)) and hAT1R-mut2+ females (4.41 ± 0.23(−), 5.23 ± 0.39(+)) females is not significant. No hypertrophy was detected in hAT1R-wt1+ females (4.32 ± 0.33(−), 4.30 ± 0.22(+)). Number of animals tested is shown in brackets. *+, expressing transgenic receptors; ‘−’, controls. *P < 0.05.

Histochemical examination revealed that cardiomyocyte cross-sectional area was increased in transgenic males (Figure 4A and B), suggesting that the increased CWI is due to cardiomyocyte hypertrophy. To look for evidence of early progression towards pathological remodelling, we visualized cell nuclei. Fibroblast nuclei could be identified by their peripheral positioning around the cardiomyocytes, whereas cardiomyocyte nuclei were less frequent, larger, and more centrally located. Of the eight transgenic hearts examined, only one showed increased focal clustering of fibroblasts that may represent initiation sites of remodelling (Figure 4C). Whether this was due to fibroblast migration or increased proliferation is unclear. Consistent with the observed increase in cardiomyocyte growth, hAT1R-mut1+ mice also showed consistently high levels of phosphorylated-mitogen-activated protein kinase (ERK1/2) in the ventricular apex (Figure 4D).

3.4 Hypertrophy is independent of hypertensive

The analysis of systolic BP indicated that the observed hypertrophy was not a consequence of haemodynamic changes (Figure 4E). However, tail-cuff plethysmography measurements provide only a snapshot reading and lack the precision to detect subtle or transient deviations. To strengthen the evidence that hypertrophy was not induced by hypertension, we evaluated BP in >12-month-old animals using implanted telemetry probes. The ability to measure BP and HR in conscious, freely moving mice also avoids the confounding effects of anaesthesia or restraint upon cardiac function. Longitudinal 24 h recordings were taken over a period of up to 6 months in hAT1R-mut1+ and control males, and no significant difference was detected between the groups (Figure 5A and B). Consistent with the results for the hAT1R-mut1 line, similar comparisons between hAT1R-mut2+ males and controls at 12 months showed no significant differences (Figure 5C and D).

3.5 Receptor activation in the heart promotes pathological remodelling

We exploited the unique properties of the N111G mutant to investigate the effects of prolonged receptor stimulation in cardiomyocytes in the absence of increased endogenous receptor activation in other cell types. Ang IV, which selectively activates the mutant receptor, was infused for 4 weeks into hAT1R-mut1+ and control males at a dose (5 μg/kg/min) that would not influence the endogenous receptors. Tests on a small number of animals implanted with telemetric probes (Figure 6A and B), and larger cohorts subjected to Millar catheter analysis (Figure 6C and D), confirmed the treatment had no influence on BP or HR and was therefore unlikely to have affected endogenous receptor activity. The Millar catheter was then advanced into the left ventricular cavity and a range of cardiovascular variables were measured (Table 1). Again, no significant difference in HR or (ventricular) pressure was detected between the groups. However, end-systolic and end-diastolic volumes were significantly increased in the hAT1R-mut1+ animals, whereas ejection fraction and pre-load-adjusted maximal power were significantly reduced. These data indicate that the left ventricular chamber in hAT1R-mut1+ males is enlarged relative to control males and suggest progression towards dilated cardiomyopathy.
Ventricular hypertrophy in hAT1R+ males is associated with increased myocyte size. (A) Mid-ventricular cryosections of hearts described in Figure 3A were stained with rhodamine-conjugated WGA and Hoechst 33258. (B) In all lines, myocyte cross-sectional area is increased in hAT1R+ animals compared with controls (hAT1R-wt1: 579±23 μm² (−), 764±44 μm² (+); hAT1R-mut1: 578±28 μm² (−), 855±75 μm² (+); hAT1R-mut2: 548±26 μm² (−), 732±37 μm² (+)). Error bars represent SEM from three animals per group, four fields of view per animal. (C) Nuclei-staining suggests focal clustering of fibroblasts in an hAT1R-mut1+ male heart (arrows in right panel), which is not evident in control hearts (left panel). (D) hAT1R-mut1+ hearts have raised levels of phosphorylated ERK1/2. Blot quantification (arbitrary units) shows that the phosphorylated/total ERK ratio is ~10-fold higher in hAT1R-mut1+ (1.40±0.20, n=3) than control (0.13±0.09, n=3) hearts. (E) No difference in systolic blood pressure is seen between controls and hAT1R-mut1+ males (104.4±3.0 (−), 106.0±3.0 (+)).

Table 1  Millar catheter assessment of cardiac function in hAT1R mut 1 transgenic mice after Ang IV infusion

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<th>Control (−) (n = 6)</th>
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Data are presented as mean ± SEM.

*P < 0.05.

**P < 0.01.
agonist induces pathological remodelling of the heart. Local AT1R activity induced by exposure to a selective agonist resulted initially in a controlled growth response. Increased receptor activation with the mutant receptor-selective antagonist Ang IV was required to initiate pathological remodelling. The cues for the infiltration of fibroblasts and the deposition of extracellular matrix in the ventricular free wall remain to be determined, but most likely stem from signals originating in compromised myocytes.

When our findings are taken together with other murine studies that have used the αMHC promoter to drive AT1R expression in cardiomyocytes, the variation between models is significant. In rats, AT1R over-expression only caused hypertrophy when the heart was artificially overloaded.32,33 In contrast, 200–400-fold over-expression in mouse cardiomyocytes, initiated during foetal development, caused pathological remodelling and heart failure within a few months of birth and increased susceptibility to arrhythmia through delayed repolarization.14,34 Further studies showed that ~30-fold over-expression was sufficient to cause ventricular hypertrophy without lethality.16 Most strikingly, two-fold up-regulation caused atrial cardiomyocyte over-proliferation and neonatal lethality, but no ventricular over-proliferation or hypertrophy.13 As this occurred before birth, it is consistent with the αMHC promoter expression profile in the developing atria where the cardiomyocyte precursors retain high differentiation and proliferation potential. Two of the reported models also identified a strong association between cardiomyocyte-specific AT1R expression and bradycardia, which may be caused by impaired atrio-ventricular node development. In all cases, the phenotype could be caused, in part, by embryonic myocardial defects.13,16

Irrespective of the variation in phenotype, over-expression in developing embryonic cardiomyocytes prior to their maturation made it unclear whether increased AT1R activity in mature cardiomyocytes would have a significant impact on outcome in the absence of developmental defects. In this study, we therefore avoided these confounding factors by restricting the receptor expression to the developed heart.

We also noted significant transgene expression in pulmonary veins. Although this activity was reported in early characterization of the αMHC promoter,14 it is rarely considered. It is possible that the lethality encountered in some previous models that have used the αMHC promoter to drive AT1R expression13,14 was caused by hyperplasia and/or hypertrophy of the pulmonary veins early in development.

In conclusion, we have demonstrated that animals in which AT1R expression is increased, only five-fold exhibit activated. These changes occur independent of sedentary BP, thus clearly separating two intrinsically linked risk factors for heart failure, namely hypertension and myocardial hypertrophy.

The expression of a similar constitutively active AT1R mutant, under the control of the endogenous AT1R promoter, was recently shown to mediate cardiac fibrosis without cardiomyocyte hypertrophy,31 which differs from our observations. However, in those experiments, the mutant receptor was expressed in many different tissues and cell types, including cardiac fibroblasts as well as cardiomyocytes (which account for ~50% of all myocardial cells) throughout development. The absence of cardiomyocyte hypertrophy, in spite of marked haemodynamic overload through systemic changes, is surprising. In our study, the receptor expression was restricted to cardiomyocytes and resulted initially in a controlled growth response. Increased receptor activation with the mutant receptor-selective agonist Ang IV was required to initiate pathological remodelling. The cues for the infiltration of fibroblasts and the deposition of extracellular matrix in the ventricular free wall remain to be determined, but most likely stem from signals originating in compromised myocytes.

Histological examination revealed further striking evidence that local receptor activation promotes pathological remodelling. Control males infused with Ang IV showed no response (Figure 6E), whereas hAT1R-mut1+ males showed increased ventricular cardiomyocyte hypertrophy and localized fibrosis (Figure 6F). The left ventricular free wall, in particular, contained dramatically enlarged cardiomyocytes, interspersed with fibrotic tissue largely devoid of heart muscle cells (Figure 6G). The regions of increased fibrosis were found to contain more cells positive for cleaved caspase-3, indicating that remodelling is progressing by the induction of apoptosis (Figure 6H–J). Thus, increased local AT1R activity induced by exposure to a selective agonist induces pathological remodelling of the heart.

4. Discussion

We have described a novel conditional mouse model of clinically relevant ventricular hypertrophy. Increased AT1R expression in adult cardiomyocytes causes hypertrophy by regulating cardiomyocyte growth, but does not progress to pathological remodelling until the receptors are further

Figure 5 Telemetry recording of blood pressure and heart rate demonstrates no significant change in 12-month-old hAT1R-mut1+ and -mut2+ males. Results are averaged over a representative 24 h period. (A) Blood pressure, hAT1R-mut1: 106 ± 2(–), 114 ± 6(+), P = 0.3. (B) Heart rate, hAT1R-mut1: 510 ± 27(–), 500 ± 8(+), P = 0.7. (C) Blood pressure, hAT1R-mut2: 110 ± 5(–), 117 ± 3(+), P = 0.4. (D) Heart rate, hAT1R-mut2: 542 ± 39(–), 516 ± 12(+), P = 0.5. Number tested is shown in brackets. ‘+’, expressing transgenic receptors; ‘+’, controls.
modest hypertrophy, characterized by increased cardiomyocyte size. This is not associated with the alteration of BP or HR. Full activation with Ang IV at levels that activate the mutant receptor without influencing native receptors (and therefore without raising systemic BP) caused increased fibrosis and impaired cardiac function. Our data are therefore consistent with the local RAS signalling acting as a sensitive and dynamic regulator of cardiomyocyte growth, which impacts on cardiac function, thus playing a significant part in the development of both cardiac hypertrophy and in progression towards heart failure.

This controllable model of cardiac remodelling is ideal for dissecting the cross-talk between cells and the signalling pathways that are activated downstream of the local RAS activity to regulate progression from normal cardiac structure and function through a state of ventricular hypertrophy and culminating in adverse remodelling and impaired function.

Supplementary material

Supplementary material is available at Cardiovascular Research online.

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References


