Transgenic Model of Aldosterone-Driven Cardiac Hypertrophy and Heart Failure

Wenning Qin, Amy E. Rudolph, Brian R. Bond, Ricardo Rocha, Eric A.G. Blomme, Joseph J. Goellner, John W. Funder, Ellen G. McMahon

Abstract—Aldosterone classically promotes unidirectional transepithelial sodium transport, thereby regulating blood volume and blood pressure. Recently, both clinical and experimental studies have suggested additional, direct roles for aldosterone in the cardiovascular system. To evaluate aldosterone activation of cardiomyocyte mineralocorticoid receptors, transgenic mice overexpressing 11β-hydroxysteroid dehydrogenase type 2 in cardiomyocytes were generated using the mouse α-myosin heavy chain promoter. This enzyme converts glucocorticoids to receptor-inactive metabolites, allowing aldosterone occupancy of cardiomyocyte mineralocorticoid receptors. Transgenic mice were normotensive but spontaneously developed cardiac hypertrophy, fibrosis, and heart failure and died prematurely on a normal salt diet. Eplerenone, a selective aldosterone blocker, ameliorated this phenotype. These studies confirm the deleterious consequences of inappropriate activation of cardiomyocyte mineralocorticoid receptors by aldosterone and reveal a tonic inhibitory role of glucocorticoids in preventing such outcomes under physiological conditions. In addition, these data support the hypothesis that aldosterone blockade may provide additional therapeutic benefit in the treatment of heart failure. (Circ Res. 2003;93:69-76.)

Key Words: 11β-hydroxysteroid dehydrogenase type 2 ■ mineralocorticoid ■ eplerenone ■ mineralocorticoid receptor ■ heart failure

Aldosterone classically promotes unidirectional transepithelial sodium transport, thereby regulating blood volume and blood pressure. Recently, both clinical and experimental studies have suggested additional, direct roles for aldosterone in the cardiovascular system. Plasma aldosterone concentrations correlate with left ventricular (LV) hypertrophy,1 vascular stiffness,2 heart failure, and mortality.3 In experimental hypertension, aldosterone produces blood pressure elevation by stimulating brain mineralocorticoid receptors (MRs)4 and, when combined with high salt intake, produces cardiac hypertrophy, fibrosis, and vascular inflammatory injury5–7 independent of blood pressure elevation.8 Moreover, when the new selective aldosterone blocker eplerenone was added to optimal medical therapy in a recently completed clinical study, morbidity and mortality were reduced in patients with acute myocardial infarction complicated by LV dysfunction and heart failure.9 The nonselective aldosterone blocker spironolactone produces striking improvements in morbidity and mortality in patients with severe heart failure.10

In various epithelial cells11–12 and vascular smooth muscle cells (VSMCs),13 expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts endogenous glucocorticoids to their receptor-inactive 11-keto analogues, thereby conferring aldosterone selectivity on MR. Both cardiomyocytes14,15 and VSMCs15 express MRs with equivalent, high affinities for aldosterone, corticosterone, and cortisol.16,17 However, cardiac expression of 11β-HSD2 is extremely low,14 such that cardiomyocyte MRs are primarily occupied by endogenous glucocorticoids that are present at higher levels than aldosterone in the blood under normal conditions.

A second difference between epithelial (and VSMC) and nonepithelial MRs is their response to occupancy by endogenous glucocorticoids (cortisol in human, corticosterone in rodent). In epithelia, glucocorticoids mimic aldosterone,18 as in the syndrome of apparent mineralocorticoid excess.19–21 In nonepithelial tissues such as cardiomyocytes, glucocorticoids do not activate MR but act as antagonists.22–25 Although the mechanism underlying this difference is unknown, it may reflect tissue-specific differences in coactivator/corepressor recruitment by MR/glucocorticoid complexes, as seen with estrogen receptors.26

To examine the direct role of aldosterone in cardiac pathophysiology, we exploited the enzymatic activity of 11β-HSD2 and generated transgenic mice that overexpressed this enzyme in cardiomyocytes, thus reducing myocardial
intracellular glucocorticoids and allowing aldosterone occupancy of cardiomyocyte MR. In another study, this approach has been used to successfully inactivate natural glucocorticoids in osteoblasts in cell culture.27

Materials and Methods

Transgenic Mice

Mouse 11β-HSD2 cDNA was isolated by reverse transcriptase-polymerase chain reaction (RT-PCR) from mouse kidney total RNA and cloned into the plasmid Clone 26 provided by Jeffrey Robbins (University of Cincinnati, Cincinnati, Ohio) to recruit the 5.4-kb mouse α-myoosin heavy chain (α-MHC) promoter. The transgenic construct was released from the prokaryotic backbone and injected into the pronucleus of C57BL/6 embryos at the one-cell stage (Charles River Laboratories, Wilmington, Mass). Transgenic mice were maintained by sibling mating and used as hemizygotes. Mice received rodent chow containing 0.32% Na+ and 0.83% K+ (No. 7012, Harland Teklad), and eplerenone was administered by chow supplemented with eplerenone at 2 mg/g (Research Diets). The daily dose was ∼200 mg/kg. All experimental procedures were approved by the Institutional Laboratory Animal Care and Use Committee of Pfizer, Inc.

Real-Time RT-PCR Analysis

Reagents, software, and equipment were purchased from Applied Biosystem. Taqman reactions were performed using one-step RT-PCR Master Mix Reagents with the ABI PRISM 7700 Sequence Detection System and analyzed using the Sequence Detection System software. Gene expression was normalized to cyclophilin. Primers and probes were based on GenBank sequences (11β-HSD2, NM_008289; α-MHC, M76601; β-MHC, L07306; atrial natriuretic peptide [ANP], K02781; collagen I, U08020; collagen III, X52046; osteopontin, X14882; aldosterone synthase, S85260; matrix metalloproteinase-9 [MMP-9], NM_013599; early growth factor response-1 [EGFR-1], NM_007913; and cyclophilin, M19533).

11β-HSD2 Enzyme Assay

Tissue homogenates were incubated for 1 hour at 37°C in 50 μL containing 20 nmol/L [1,2,6,7-3H] corticosterone (Amersham Pharmacia Biotech, ∼70 Ci/mmol), 1% ethanol, 0.2% BSA, and 1 mmol/L NAD (Sigma). Steroids were extracted with ethyl acetate and resolved by thin-layer chromatography with chloroform:95% ethanol (92:8). [3H]-11-dehydrocorticosterone was identified under UV with unlabeled carrier and quantitated by scintillography. Specific activity was calculated after subtraction of background turnover.

In Situ Hybridization

Complementary RNA (cRNA) probes were generated using in vitro transcription from a 414-bp cDNA template from the mouse 11β-HSD2 (GenBank accession No. NM_008289.1) and labeled with 3P-UTP (NEN Life Science Products). Sections were processed by standard histological techniques and hybridized overnight at 55°C in buffer (50% formamide, 2×SSC, 10% dextran sulfate) containing tRNA (50 μg/mL) and cRNA probe. Signal was detected by coating slides with NTB-2 autoradiographic emulsion (Eastman Kodak) and exposing the slides at 4°C for 1 to 2 weeks before development. Counterstaining was with H&E.

Immunohistochemistry

A primary polyclonal antibody was generated in rabbit against the peptide AAQPPRSRYYPGRGLC from A331 to L346 of the mouse 11β-HSD2 (NP_032315.1) and provided by Zygmun Krozowski (Baker Heart Research Institute, Melbourne, Australia). A biotinylated anti-rabbit IgG was used as the secondary antibody. Sections were incubated with streptavidin horseradish-peroxidase (Vector Laboratories) and visualized by DAB chromogen (Vector). Counterstaining was with hematoxylin.

Collagen Content

Sections were stained with Picrosirius Red (Sigma Aldrich), and a spot RT color digital camera was used to capture 18 to 20 fields from the left ventricle of the heart sample. The images were then analyzed using Optimus v6.51 image analysis software, and the percentage of tissue that is collagen was determined.

Plasma Electrolytes and Brain Natriuretic Peptide

Plasma Na+ and K+ concentrations were determined by flame photometry (Instrumentation Laboratory), and plasma brain natriuretic peptide (BNP) concentrations were measured using the Luminesx system (Lumines Incorp) with a rabbit anti-rat BNP45 (Peninsula Laboratories, San Carlos, Calif).

Systolic Blood Pressure

Mice were trained for 6 days, and measurements were obtained over the next 6 days using a Visitech tail cuff system (Visitech Systems). For data collection, mice were placed on a heated platform (100°F) in a restrainer. A minimum of five preliminary cycles was performed before collecting 10 measurements for each mouse.

Echocardiography

Mice were lightly anesthetized with 1% to 2% isoflurane. Echocardiographic images were generated using a Sonos 5500 echocardiographic system with a 15-MHz linear-array transducer (Agilent). Two-dimensional parasternal long- and short-axis images of left ventricle were obtained, and 2D, targeted M-mode tracings from the parasternal short-axis view at the level of the papillary muscles were recorded (swEEP speed of 150 mm/s). LV area at systole (LVAS) and LV area at diastole (LVAD) were measured directly, and LV end systolic volume (ESV) and end diastolic volume (EDV) were calculated via the method of discs from areas. Fractional shortening (FS) was calculated from the following equation: (LVIdd−LVIds)/LVIdd×100, where LVIdd and LVIds are end diastolic and end systolic LV internal dimensions; and ejection fraction (EF) was calculated from the following equation: (EDV−ESV)/EDV×100. All measurements were collected by the leading-edge method as recommended by the American Society for Echocardiography.

Statistical Analysis

Treatment group means were compared using one-way ANOVA of the raw data and by the least-significant differences method, with the pooled within-group mean square error as the common estimate of the variance for all mean comparisons. Estimates of variance by one-way ANOVA were obtained, and two-sided comparisons for all analyses were used.

Results

Transgenic Mice Overexpressing 11β-HSD2 in Cardiomyocytes Developed Cardiac Hypertrophy, Fibrosis, and Heart Failure

A mouse line that carries the transgene containing the 5.4-kb mouse α-MHC promoter26 placed 5’ to the mouse 11β-HSD2 cDNA in C57BL/6 background was created, and seven independent founder lines were obtained (Figure 1A). Based on real-time RT-PCR analysis, these founder lines had different copy numbers of the transgene (line 323, 45 copies; line 324, 2; line 325, 15; line 326, 29; line 327, 1; line 328, 4; and line 490, 27). Founder 490 died at 4.5 months of age of heart failure. At the time of death, she had a heart weight/body weight ratio of 17.5 mg/g, compared with that of 6.4 mg/g of a sex-matched, nontransgenic (non-TG) littermate. Founder 323 died at 3 months of age and was not analyzed. Founder 324 was infertile and not analyzed. At 5 months of age, cardiac 11β-HSD2 expression increased
The 11β-HSD2 Gene Was Selectively Upregulated in Cardiomyocytes

In line 326 mice, the highest levels of 11β-HSD2 induction were seen in the heart (Figure 1B), with low-level induction observed in lung, liver, spleen, brain, and skeletal muscle and no induction in kidney and colon (Figure 1C). In a previous study,28 the α-MHC promoter directed gene expression to the striated muscle layer (pulmonary myocardium) of the vein in the lung and may be the cell source for induced 11β-HSD2 expression in the lung. Although mRNA levels of 11β-HSD2 were elevated three to four orders of magnitude in hearts from non-TG mice, with no increased activity in kidney from non-TG mice, with no increased activity in kidney (n=2), tissue homogenates were incubated with [1,2,6,7-3H]corticosterone and NAD. Steroids were extracted and resolved by thin-layer chromatography, [3H]-11-dehydrocorticosterone was identified under UV and quantitated by scintillography. Specific activity was calculated after subtraction of background turnover. Open bar, non-TG mice; filled bar, TG mice.

Line 326 Mice Died Prematurely at 4 to 6 Months of Age of Heart Failure

Mice from line 326 developed progressive heart failure characterized by marked dilated cardiac hypertrophy and premature death at 4 to 6 months of age (compare Figure 3B with 3A). On postmortem examination, clinical signs of heart failure were evident, such as the presence of pleural effusions and significant cardiac enlargement. All four chambers were markedly enlarged, with the heart occupying nearly the entire chest cavity. On histological examination, significant cardiomyocyte hypertrophy was evident and accompanied by extensive interstitial fibrosis (Figure 3D). Interestingly, coronary arteries did not show either endothelial or medial injury or evidence of perivascular fibrosis, suggesting that cardiomyocytes are selectively affected in this model (compare Figure 3D with 3C). This phenotype contrasts strikingly with the marked vascular inflammation and vascular remodeling associated with cardiomyocyte injury in rats when aldosterone was administered with high salt intake.7
Cardiac Structural and Functional Changes in Line 326 Mice
Mice at 3.5 months of age were examined extensively (Table). Systolic blood pressure (SBP) was unchanged in TG mice compared with non-TG mice under control conditions. The heart weight to body weight ratio (HW/BW) was increased more than 2-fold in TG mice compared with non-TG mice. Echocardiographic evaluation revealed a dramatic increase in LV area both at systole (LVAS) and diastole (LVAD). Even greater increases were observed in LV volume at systole and diastole. Cardiac function was also severely compromised, as evidenced by decreased fractional shortening (FS) and reduced ejection fraction (EF).

The Selective Aldosterone Blocker Eplerenone Significantly Attenuated the Structural and Functional Changes in 11β-HSD2 Transgenic Mice
Under physiological conditions, cardiac MRs are overwhelmingly occupied by corticosterone. It was reasoned that by converting corticosterone into 11-dehydrocorticosterone, cardiomyocyte-specific overexpression of 11β-HSD2 would permit aldosterone to activate cardiomyocyte MR, leading to heart failure. To test this hypothesis, we randomized non-TG and line 326 TG mice to receive either regular chow or chow supplemented with the selective aldosterone blocker eplerenone29 from 1 month to 3.5 months of age (~200 mg/kg per d).

Eplerenone in non-TG mice did not significantly alter SBP or cardiac structure or function (Table). In TG mice,
Plots of the TG and non-TG Mice Treated With Eplerenone

<table>
<thead>
<tr>
<th></th>
<th>Non-TG</th>
<th>Eplerenone</th>
<th>TG</th>
<th>Eplerenone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=6</td>
<td>n=7</td>
<td>n=6</td>
<td>n=9</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>110±1</td>
<td>106±2</td>
<td>105±2</td>
<td>104±2</td>
</tr>
<tr>
<td>HW/BW, mg/g</td>
<td>6.4±0.3</td>
<td>6.4±0.3</td>
<td>14.4±1.6</td>
<td>9.9±0.7†</td>
</tr>
<tr>
<td>KW/BW, mg/g</td>
<td>7.2±0.3</td>
<td>6.4±0.3</td>
<td>5.9±0.3</td>
<td>6.5±0.3</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>n=7</td>
<td>n=7</td>
<td>n=9</td>
<td>n=11</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>524±12</td>
<td>514±10</td>
<td>495±12</td>
<td>484±11</td>
</tr>
<tr>
<td>EF, %</td>
<td>72.7±4.0</td>
<td>71.6±2.1</td>
<td>31.6±4.2</td>
<td>48.1±4.4†</td>
</tr>
<tr>
<td>FS, %</td>
<td>54.0±2.5</td>
<td>54.2±1.6</td>
<td>19.3±1.6</td>
<td>30.7±3.2‡</td>
</tr>
<tr>
<td>LVAD, cm²</td>
<td>0.12±0.00</td>
<td>0.11±0.01</td>
<td>0.26±0.02</td>
<td>0.16±0.01†</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>0.02±0.00</td>
<td>0.02±0.00</td>
<td>0.08±0.01</td>
<td>0.03±0.00†</td>
</tr>
<tr>
<td>LVAS, cm²</td>
<td>0.05±0.01</td>
<td>0.05±0.01</td>
<td>0.21±0.02</td>
<td>0.11±0.01†</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>0.01±0.00</td>
<td>0.01±0.00</td>
<td>0.06±0.01</td>
<td>0.02±0.00‡</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td>n=7</td>
<td>n=8</td>
<td>n=11</td>
<td>n=12</td>
</tr>
<tr>
<td>Na⁺, mmol/L</td>
<td>150±1</td>
<td>145±4</td>
<td>149±2</td>
<td>142±4</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>5.9±0.3</td>
<td>5.5±0.3</td>
<td>5.3±0.1</td>
<td>6.4±0.3‡</td>
</tr>
<tr>
<td>BNP, ng/mL</td>
<td>1.8±0.4</td>
<td>1.8±0.3</td>
<td>2.0±0.5</td>
<td>2.2±0.4</td>
</tr>
</tbody>
</table>

Statistically significant differences between TG control and TG eplerenone are indicated. †P<0.01; ‡P<0.001. SBP indicates systolic blood pressure; HW/BW, heart weight/body weight ratio; KW/BW, kidney weight/body weight ratio; HR, heart rate; EF, ejection fraction; FS, fractional shortening; LVAD, left ventricular area at the end of diastole; EDV, end-diastolic volume; LVAS, left ventricular area at the end of systole; ESV, end-systolic volume; Na⁺, plasma sodium concentration; K⁺, plasma potassium concentration; and BNP, plasma concentration of brain natriuretic peptide.

Eplerenone also did not affect SBP but attenuated the development of cardiac hypertrophy as indicated by a reduced HW/BW ratio (Table). Systolic and diastolic LV areas and ESV and EDV were all significantly reduced by eplerenone (Table). Significantly improved indices of cardiac function, such as EF and FS, were also noted. Among all parameters, improvement in ESV and EDV were most striking such that TG eplerenone values were not statistically different from non-TG controls (Table).

Plasma sodium concentration did not differ between genotypes or treatments (Table). In contrast, there was a rise in plasma potassium concentration with eplerenone administration in TG mice, which was not observed in non-TG mice receiving eplerenone (Table). Although this presumed increased renal sensitivity to eplerenone might reflect the phenotype in TG mice, the underlying neurohormonal mechanism remains unclear. In particular, it did not seem to be attributable to differences in plasma BNP levels, which were indistinguishable among the four groups.

Eplerenone Improved Hypertrophy and Heart Failure–Associated Genes in 11β-HSD2 Transgenic Mice

Using real-time RT-PCR, we analyzed gene expression in line 326 mice (Figure 4, compare TG to non-TG controls) and found that marker genes of mechanical overload, including β-MHC and ANP, were elevated, whereas α-MHC was downregulated. Consistent with cardiac fibrosis, expression of collagen types I and III was increased. In addition, expression of the proinflammatory cytokine osteopontin was increased. Interestingly, MMP-9 was downregulated compared with non-TG controls, whereas changes in aldosterone synthase and EGR-1 were similar in TG control and non-TG control mice.

Consistent with a role of aldosterone in this heart failure model, eplerenone improved the expression profile of genes associated with mechanical overload and heart failure in TG mice (Figure 4, compare TG eplerenone with TG control). Expression of the α-MHC gene was elevated whereas the expression of osteopontin and collagen III were reduced with eplerenone treatment. Changes in β-MHC, ANP, and collagen type I expression were not statistically significant. Aldosterone synthase (CYP11B2) levels were elevated in TG myocardium by eplerenone, perhaps reflecting the increase in plasma potassium in these mice. Although expression of endogenous 11β-HSD2 was not altered by eplerenone in non-TG mice, cardiac 11β-HSD2 expression was increased in TG mice. This response is consistent with the elevated α-MHC promoter activity in TG mice treated with eplerenone.

Discussion

Cardiomyocyte MRs are normally occupied by endogenous glucocorticoids under physiological conditions. However, in pathophysiological states, it has been hypothesized that mineralocorticoids can access cardiac MR and produce cardiac damage. The current 11β-HSD2 overexpression and aldosterone blockade study supports this hypothesis and is consistent with previous in vitro and in vivo studies in rat models.22–25 The demonstration that eplerenone can ameliorate the effects of 11β-HSD2 overexpression is evidence for a specific effect via MR rather than a nonspecific effect on cardiomyocyte metabolic state, as may be the case in other studies.30,31 It remains to be understood how the 11β-HSD2 expression correlates with cardiac hypertrophy and failure in a clinical setting, although its association with human hypertension is well documented. For example, mutations in the 11β-HSD2 gene lead to apparent mineralocorticoid excess syndrome.19–21 In addition, the number of CA repeats located in intron 1 of the human 11β-HSD2 gene is correlated with salt-sensitive human hypertension.32

In the present study, the myocardial vasculature was histologically unaffected by cardiomyocyte overexpression of 11β-HSD2, with the detrimental effect confined to the cardiomyocytes. These findings are in striking contrast to studies using mineralocorticoid/salt administration in rats, where the salient response is that of vascular inflammation and vascular remodeling in the heart, associated with macrophage infiltration of the vascular and interstitial compartments and the expression of a range of proinflammatory cytokines.8 This phenotype disparity may result from limiting genetic manipulation in our study to cardiomyocytes, without involvement of the coronary vasculature. Alternatively, this difference may result from the apparent need for elevated...
dietary sodium intake to manifest aldosterone-driven vascular damage.33

The distinction between the cardiomyocyte response in the current study and in experiments involving mineralocorticoïd/salt excess suggests separate cardiovascular roles for cardiomyocyte and VSMC MR. VSMCs express 11β-HSD234 and thus potentially represent an aldosterone target tissue like the renal epithelial cell, where MRs are aldosterone-selective as a consequence of high levels of 11β-HSD2 expression. This concept is additionally supported by previous studies where administration of the 11β-HSD2 inhibitor carbenoxolone to rats induced coronary vascular inflammation that could be blocked by eplerenone, reflecting glucocorticoid activation of the otherwise inaccessible VSMC MRs.34

In contrast, in the cardiomyocyte, 11β-HSD2 is not normally expressed, and thus MRs are unprotected. Importantly, in such nonepithelial cells, glucocorticoids act as antagonists rather than agonists of MR.22,23 In the cardiomyocyte, overexpression of 11β-HSD2 produces pathophysiology, reflecting inappropriate occupancy and activation of MR by circumventing the presumed tonic inhibitory (or physiological antagonist) role of glucocorticoids in unprotected MRs under physiological conditions. An alternative explanation is that the pathology we observed in this model from depletion of cardiac glucocorticoids by overexpression of 11β-HSD2 reflects a reduction in glucocorticoid receptor (GR) occupancy by corticosterone rather than MR occupancy by aldosterone. However, this interpretation is not supported by previous studies using the GR antagonist RU486, where a cardiac phenotype was not observed.25

Corticosteroids are reported to provide acute cardiovascular protection by nontranscriptional activation of endothelial nitric oxide synthase.35 Consistent with this notion, the present study suggests that corticosteroids may exert a tonic inhibitory role, preventing MR from being activated by aldosterone. However, this may be a minimalist interpretation of the data, given the evolutionary persistence of unprotected MR in the heart. Because such MRs are unprotected, they normally will be occupied by glucocorticoids, given that the levels of free glucocorticoids are ≥100 times higher than those of aldosterone and that diurnal variation in cortisol and aldosterone tracks in parallel. The affinity of MR for cortisol and corticosterone is one to two orders of magnitude higher than of GR. Unprotected MRs are thus always substantially (≥90%) occupied by glucocorticoids, even at nadir levels.36

When 11β-HSD2 is operating normally, it cannot sufficiently convert cortisol to cortisone to exclude it from renal MR. In the rat, in vivo direct binding studies have demonstrated that most kidney MRs under normal conditions are occupied by glucocorticoids, but these MR-glucocorticoid complexes are not transcriptionally active.37 However, when the enzyme is absent or blocked by carbenoxolone or glycyrhizinic acid, glucocorticoid-occupied renal MRs become transcriptionally active. One possible explanation for this phenomenon lies in the fact that the operation of 11β-HSD2 involves not only the conversion of cortisol to cortisone but of the cosubstrate NAD⁺ to NADH. Thus, if MR-glucocorticoid complexes are inactive under conditions of high intracellular NADH, as is the case when 11β-HSD2 is operant, but are active when the equilibrium swings toward NAD⁺, then the dilemma noted above may be resolved. Redox-dependent glucocorticoid receptor–mediated responses to dexamethasone have been previously described.38,39 Such a possibility for MR may also point the way to a physiological role for MR-glucocorticoid complexes in the cardiomyocyte, that of acting as always-occupied intracellular redox sensors, as seen with the GRs.

The present study provides compelling evidence that aldosterone activation of cardiomyocyte MR leads to myocardial...
Injury and ultimately heart failure. In congestive heart failure, plasma aldosterone levels are often elevated and correlate with mortality. In a comparison study in which patients with primary aldosteronism and essential hypertension were matched for severity and duration of hypertension, a higher incidence and more severe LV hypertrophy and remodeling was demonstrated in patients with primary aldosteronism. Even in patients with moderate essential hypertension, circulating aldosterone levels correlate with LV mass index and mean plasma levels are only slightly increased over normal. In addition, some reports suggest that local aldosterone production may be increased in rat heart after myocardial infarction, in the failing human heart, and in hearts from hypertensive patients without LV systolic dysfunction, although possible pathophysiological roles for cardiac aldosterone synthesis remain to be established. Although the deleterious consequences of aldosterone activation of cardiovascular MR are clearly evident, we do not yet understand how activation of MR produces cardiac injury.

Acknowledgments

This work was supported by Pfizer Global R&D. We acknowledge Dr Arnold Strauss for his critical review of the manuscript. We would also like to thank Dr Zygmunt Krozowski (Baker Heart Research Institute, Melbourne, Australia) for the 11β-HSD2 antibody, Michelle Noll (pronuclear injection), Carmen Thielemier (colony management), Ryan Philip and Mei Han (genotyping), Carmen Thielemier (histology), and James Kiefer (art work) for their excellent technical assistance.

References


Transgenic Model of Aldosterone-Driven Cardiac Hypertrophy and Heart Failure
Wenning Qin, Amy E. Rudolph, Brian R. Bond, Ricardo Rocha, Eric A.G. Blomme, Joseph J. Goellner, John W. Funder and Ellen G. McMahon

Circ Res. 2003;93:69-76; originally published online June 5, 2003;
doi: 10.1161/01.RES.0000080521.15238.E5
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/93/1/69

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/