Physiological Impact of Increased Expression of the AT$_1$ Angiotensin Receptor

Thu H. Le, Hyung-Suk Kim, Andrew M. Allen, Robert F. Spurney, Oliver Smithies, Thomas M. Coffman

Abstract—To test the effect of increased AT$_1$ receptor expression on blood pressure, we used gene targeting to generate mouse lines with a tandem duplication of the AT$_{1A}$ receptor gene locus (Agtr1a) along with >10 kb of 5’ flanking DNA. By successive breeding, we generated mice with 3 and 4 copies of the Agtr1a gene locus on an inbred 129/Sv background. AT$_{1A}$ mRNA expression and AT$_1$-specific binding of $^{125}$I-angiotensin II were increased in proportion to Agtr1a gene copy number. These animals survived in expected numbers, and their body, heart, and kidney weights were similar to wild-type, 2-copy control mice. Pressor responses to angiotensin II were blunted in the 4-copy mice compared with control mice. In male mice, there was no correlation between resting blood pressure and Agtr1a gene copy number or AT$_{1A}$ mRNA levels. However, in female mice, there was a highly significant positive correlation between blood pressure and AT$_{1A}$ receptor expression, paralleled by significant increases in aldosterone synthase expression with increase in gene copy number. Furthermore, in female but not male mice, there was a positive correlation between kallikrein and AT$_{1A}$ receptor mRNA levels and an inverse correlation between renin mRNA and Agtr1a copy number. Thus, in female but not male mice, genetic variants that increase expression of AT$_1$ receptors affect blood pressure and gene expression programs. The impact of enhanced AT$_1$ receptor expression on blood pressure may be blunted by systemic compensatory responses and altered signal-effector coupling in the vasculature. (Hypertension. 2003;42:507-514.)

Key Words: hypertension, renal α1 renin α1 aldosterone α1 mice α1 gender

The renin-angiotensin system (RAS) plays a critical role in the regulation of blood pressure and sodium homeostasis. Enhanced activity of the RAS causes hypertension and end-organ injury. Variations in genes encoding components of the RAS have been associated with hypertension in human populations. For example, the M235T variant of the gene encoding angiotensinogen, the protein precursor of angiotensin II, has been associated with elevated plasma angiotensinogen levels and essential hypertension in white American and French populations. This allele is in linkage disequilibrium with a single nucleotide substitution in the promoter region of the angiotensinogen gene that appears to enhance transcriptional efficiency. Direct proof of a causal relation between Agt genotypes and blood pressures has been established by using genetically engineered mouse models.

The major physiological actions of the RAS are mediated through the type 1 (AT$_1$) receptor, and clinical studies have demonstrated that pharmacological blockade of the AT$_1$ receptor effectively lowers blood pressure and protects against end-organ damage. Rodents have two AT$_1$ receptor isoforms, AT$_{1A}$ and AT$_{1B}$, which are encoded by distinct genes. In most tissues, expression of the AT$_{1A}$ receptor far exceeds that of the AT$_{1B}$ receptor, and the AT$_{1A}$ receptor is considered to be the murine homologue of the human AT$_1$ receptor. In previous studies, we found that incremental reductions in AT$_{1A}$ receptor gene expression implemented through gene targeting caused a proportional lowering of resting blood pressure. For example, in heterozygous Agtr1a$^+/-$ mice, a 50% reduction in AT$_{1A}$ receptor expression lowers systolic blood pressure by 12 mm Hg compared with control mice; the complete absence of AT$_{1A}$ receptors in Agtr1a$^{-/-}$ mice is associated with a further lowering of blood pressure. This demonstration that reduced levels of AT$_{1A}$ receptor gene expression affect blood pressure suggests that naturally occurring variants of the Agtr1a gene locus that increase the level of receptor expression could positively affect resting blood pressure.

To determine whether increased levels of AT$_{1A}$ receptor expression would increase blood pressure, we generated mice with a targeted duplication of the Agtr1a gene locus and examined the physiological effects of the resulting quantitative variation of the AT$_{1A}$ receptor gene expression. Using this model, we found that the impact of increased AT$_1$ receptor expression on blood pressure is complex and that
Ligand Binding Assays
The density of AT\textsubscript{1} receptors in the kidney was determined by quantitative in vitro autoradiography as described previously.\textsuperscript{14} Twenty-micrometer kidney sections were incubated with \textsuperscript{3}H-[Sar\ Ile\ II] angiotensin II in the presence of the selective AT\textsubscript{1} antagonist candesartan (1 \textmu mol/L, Astra H"assle) or the AT\textsubscript{2} antagonist PD123319 (10 \textmu mol/L, Parke-Davis). The sections were then exposed to x-ray film (UM-MA HC medical x-ray film, Fuji Co). Radioactivity standards were exposed simultaneously, which then allowed the optical densities of the radiographic images to be converted into radioactivity levels (disintegrations per minute, dpm), using a computerized imaging system (MCID Imaging Research).

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\begin{align*}
\text{[3H]Angiotensin II Binding Studies} \\
\text{Kidneys from 2-copy or 3-copy mice (n=6) were removed and placed in ice-cold ×1 Dulbecco’s PBS buffer. Mouse glomeruli were isolated as described in detail previously.}\textsuperscript{13} Equal binding curves were analyzed by Scatchard method to estimate Bmax and equilibrium Kd by fitting the data to a nonlinear model with the use of the ENZFITTER computer program (Elsevier-Biosoft).
\end{align*}
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\begin{align*}
\text{Angiotensin II Infusions} \\
\text{We measured acute pressor response to 0.1, 1, and 10 \textmu g/kg angiotensin II in (+/+), (2Agtr1a/+), and (2Agtr1a/2Agtr1a) animals as described.}\textsuperscript{9} To inhibit endogenous angiotensin II production, ACE inhibitor enalapril (30 mg/kg per day orally) was administered for 2 days before study, and an additional 10 mg/kg IV was given at the start of the study.
\end{align*}
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\begin{align*}
\text{Measurements of Resting Blood Pressure} \\
\text{Systolic blood pressures were measured in conscious mice with the use of a computerized tail-cuff system (Visitech Systems) that has been validated and described previously.}\textsuperscript{16}
\end{align*}
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\begin{align*}
\text{Quantification of mRNA Expression by Real-Time RT-PCR} \\
\text{Relative levels of mRNA for renin, the AT\textsubscript{1} receptor, aldosterone synthase, and kallikrein were determined by real-time RT-PCR with the ABI Prism 7700 Sequence Detection System as described, and the nucleotide sequences of the PCR primers and their fluorogenic probes have been published previously.}\textsuperscript{17}
\end{align*}
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\begin{align*}
\text{Data Analysis} \\
\text{For comparisons between groups, statistical significance was assessed by nonparametric Mann-Whitney rank sum test. Linear regression analysis was used to correlate the relation between response variable and single predictor variable (Minitab Statistical Software).}
\end{align*}
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\begin{align*}
\text{Results} \\
\text{Normal Survival of Mice With 3 or 4 Copies of the Agtr1a Gene Locus} \\
\text{We assessed survival and general characteristics at weaning of 156 consecutive progeny from matings of 3-copy (2Agtr1a/+×3-copy (2Agtr1a/+) animals. The proportions of surviving 2- (+/+), 3- (2Agtr1a/+), and 4-copy (2Agtr1a/2Agtr1a) mice were 20.5\%, 53.8\%, and 25.6\%, respectively. This distribution did not differ significantly from predicted (25%/50%/25%). Thus, an increased number of Agtr1a gene copies does not affect survival. Furthermore, growth, vigor, and fertility of 3- and 4-copy mice were indistinguishable from their (+/+).}
\end{align*}
\]
**Figure 2.** Effect of *Agrt1a* gene copy number on AT₁a mRNA expression. AT₁a mRNA levels were obtained from kidneys of 2-copy (n=25), 3-copy (n=26), and 4-copy mice (n=26). Mean is indicated by solid black circle ●. Median is indicated by horizontal line. Whiskers (vertical lines) extend to highest and lowest values. †p<0.006 vs 2-copy mice, ‡p<0.007 vs 3-copy mice.

**Figure 3.** a, Representative picture of ¹²⁵I-[Sar¹,Ile⁸] angiotensin II binding assays in kidney tissues. Kidney sections were from *Agrt1a* knockout (for negative control) (A) and 2-copy (B), 3-copy (C), and 4-copy (D) mice. b, Effect of *Agrt1a* gene copy number on angiotensin binding sites, measured by ¹²⁵I-angiotensin II binding. Ligand binding density is expressed as disintegrations per minute (DPM)/mm². Mean is indicated by solid black circle ●. Median is indicated by horizontal line. Whiskers (vertical lines) extend to highest and lowest values. †p=0.009 vs 2-copy, ‡p<0.006 vs 3-copy.

**AT₁a Receptor mRNA Levels and *Agrt1a* Genotype**

To assess AT₁a receptor mRNA expression, we isolated RNA from kidney tissues of male and female mice of all three genotypes and measured AT₁a mRNA levels by real-time PCR. As shown in Figure 2, there was a stepwise increase in AT₁a receptor mRNA expression with increasing *Agrt1a* gene copy number. AT₁a receptor mRNA levels were significantly higher in 3-copy (2Agtr1a/−/) mice (10.8±0.3 pg/µg total RNA) than in the 2-copy (+/+ ) mice (9.3±0.3 pg/µg total RNA; P<0.002), and there was a further increase in AT₁a mRNA levels in the 4-copy (2Agtr1a/2Agtr1a) mice (12.3±0.4 pg/µg total RNA; P<0.007 versus the 3-copy (2Agtr1a/+ ) group). By linear regression analysis (not shown), there was a significant positive correlation between AT₁a receptor mRNA levels and the number of *Agrt1a* genes (R²=0.313; P<0.0005). When expressed as percentages of the mean AT₁a receptor mRNA level, assigning a value of 100% to the 2-copy (+/+ ) animals, the AT₁a mRNA expression in the 3-copy animals is ~116% of normal and ~133% in the 4-copy animals. As shown in the Table, the patterns of AT₁a receptor mRNA expression in kidney did not differ significantly in females and males.

**Ligand Binding Assays**

To determine whether the *Agrt1a* gene duplication increases angiotensin binding sites, we compared ¹²⁵I-angiotensin II binding in tissues from 2-copy (+/+ ), 3-copy (2Agtr1a/+ ), and 4-copy (2Agtr1a/2Agtr1a) mice. As shown in Figure 3, there was a general increase in ¹²⁵I-[Sar¹,Ile⁸] Ang II binding with increasing *Agrt1a* gene copies. To quantify and compare the levels of AT₁-specific binding between the groups, glomerular binding densities were measured as disintegrations per minute (dpm)/mm² (Figure 3b). This analysis was facilitated by the high levels of discrete binding in glomeruli. Similar to the patterns of AT₁a mRNA expression, ¹²⁵I-Ang II glomerular binding densities were significantly higher in the 3-copy (2Agtr1a/+) mice (870±27 dpm/mm²) than in 2-copy (+/+ ) animals (764±15 dpm/mm²; P=0.009) and were further increased in the 4-copy (2Agtr1a/2Agtr1a) mice (1056±38 dpm/mm²; P<0.006 versus the 3-copy group). The proportional percent increases in glomerular binding densities, 112% for the 3-copy group and 140% for the 4-copy group, paralleled the increases in AT₁a receptor mRNA levels that we observed. Similar patterns were observed for binding densities in nonglomerular regions of the renal cortex (data not shown).

The effects of increasing the number of *Agrt1a* gene copies was also assessed by Scatchard analysis performed in isolated preparations of renal glomeruli of radioligand binding experiments using [³H]Angiotensin II. As shown in Figure 4, Bmax was significantly increased in glomeruli from 3-copy

**AT₁a mRNA Expression According to *Agrt1a* Genotype and Gender**

<table>
<thead>
<tr>
<th><em>Agrt1a</em> Genotype</th>
<th>2-Copy</th>
<th>3-Copy</th>
<th>4-Copy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9.3±0.5 (12)</td>
<td>10.3±0.3 (14)</td>
<td>12.9±0.3 (12)</td>
</tr>
<tr>
<td>Female</td>
<td>9.2±0.5 (12)</td>
<td>11.4±0.5 (10)</td>
<td>11.5±0.7 (13)</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD, pg/µg total RNA. Number of mice shown in parentheses. P>0.1 for male vs female in each genotype.
cate measurements for a typical experiment using both kidneys groups (7.9 versus 8.0 nmol). The Bmax and Kd protein and 7.9 nmol for 3-copy mice. fmol/mg protein and 8.0 nmol for 2-copy mice and 786 fmol/mg does not affect binding affinities for angiotensin II.

Gene duplication increases levels of receptor expression, it findings in mouse glomeruli. 15 This indicates that while the obtained in the present studies were similar to our previous Responses to Angiotensin II (vertical lines) extend to highest and lowest values. solid circle. Median is indicated by horizontal line. Whiskers 

AT1A Receptor mRNA Expression in the Vasculature and Heart

Because pressor responses to low-dose Ang II infusion were attenuated in the 4-copy mice compared with wild-type, we next examined AT1A receptor mRNA levels in the left ventricle and aorta to determine whether there was any downregulation in receptor expression in vascular tissues that could account for the attenuated pressor response. In the 4-copy mice, AT1A receptor expression levels in the aorta of 4-copy animals were twice as high as in the 2-copy animals (1.03±0.19 pg/μg total RNA versus 0.50±0.07 pg/μg total RNA, P<0.02). Similarly, in the left ventricle, AT1A receptor mRNA levels were more than twice that of 2-copy animals (60.0±6.5 pg/μg total RNA versus 26.3±3.7 pg/μg total RNA, P=0.003). In the 4-copy animals, the augmentation of AT1A mRNA levels in the heart and vasculature (>200% of control levels) was significantly greater than in the kidney (≈133%).

Blood Pressure and Agtr1a Genotype

to determine the effects of increased AT1A receptor expression on resting blood pressure, we compared the systolic blood pressures of 2- (+/+), 3- (2Agtr1a/2Agtr1a), and 4-copy mice (2Agtr1a/2Agtr1a). Because of known gender differences in the regulation of components of the renin-angiotensin system and in the epidemiology of hypertension, we also examined correlations between blood pressure and Agtr1a genotypes in the entire cohort and separately in male and female mice. In addition, because there were a range of AT1A mRNA expression levels among individual animals within the same genotype, we also examined correlations between blood pressure and individual AT1A mRNA levels. In the combined group, there was a general correlation between the mean level of blood pressure and gene copy number (102±2, 104±2, and 106±2 mm Hg for 2-, 3-, and 4-copy mice, respectively), but these differences were not statistically significant. When blood pressure was compared in the male mice, there was no apparent association between the mean blood pressure and Agtr1a gene copy number (107±4 [n=12] versus 104±2 [n=19] versus 107±4 [n=13] mm Hg for 2-, 3-, and 4-copy mice, respectively) and no significant correlation between individual values of blood pressure and genotype or AT1A mRNA levels (data not shown). In contrast, blood pressure differences between genotypes were significantly correlated in female mice (99±2 [n=19], 104±3 [n=15], and 105±3 mm Hg [n=13] for 2-, 3-, and 4-copy mice, respectively; P=0.03 for 2-copy versus 3- and P=0.02 for 2-copy versus 4- copy; Figure 6a). Moreover, as shown in Figure 6b, there was a highly significant positive correlation
between blood pressure and AT\textsubscript{1A} receptor expression ($P=0.003$) in the female animals.

**Effects of **\textit{Agtr1a}** Genotype on Gene Expression Programs**

To determine whether changes in \textit{Agtr1a} gene copy number would lead to changes in the expression of other genes related to blood pressure regulation, we examined correlations between genotype, AT\textsubscript{1A} mRNA levels, and mRNA levels for three representative genes that are involved in blood pressure homeostasis: aldosterone synthase, renin, and kallikrein. We chose to specifically examine these three genes because of our previous observations of significant gender effects and interactions between their expressions and angiotensinogen genotype in mice.\textsuperscript{17} In male animals, we found no correlation between \textit{Agtr1a} copy number or AT\textsubscript{1A} receptor mRNA level and mRNA levels of aldosterone synthase, renin, or kallikrein. In contrast, in female animals (Figure 7a), there were significant stepwise increases in aldosterone synthase mRNA expression with increase in \textit{Agtr1a} copy number (571±71 [n=8], 592±34 [n=5], and 760±23 pg/μg total mRNA [n=7] for the 2-, 3-, and 4-copy groups, respectively, \(P<0.04\) for 2- versus 4-copy), and there were significant stepwise reductions in renin mRNA levels between the \textit{Agtr1a} genotypes (27±3 [n=8], 25±3 [n=5], and 18±2 [n=7] pg/μg total mRNA for the 2-, 3-, and 4-copy groups, respectively; \(P=0.006\) for 2- versus 4-copy and \(P<0.04\) for 3- versus 4-copy; Figure 7b). Moreover, in female mice, there was a highly significant correlation between kallikrein mRNA levels and AT\textsubscript{1A} receptor mRNA levels ($R=0.504; P=0.001$; Figure 7c).

**Discussion**

To understand the possible physiological consequences of genetic variants that increase AT\textsubscript{1} receptor expression, we generated mouse lines with 3 and 4 copies of the \textit{Agtr1a} gene locus on an inbred genetic background. In these animals, AT\textsubscript{1A} gene expression is under the control of the natural \textit{Agtr1a} promoter. However, the consequences of increasing \textit{Agtr1a} gene copies on AT\textsubscript{1A} mRNA expression varied in different tissues. In the vasculature and the heart, increasing the number of \textit{Agtr1a} gene copies from 2 to 4 caused a proportional doubling of AT\textsubscript{1A} mRNA expression levels to 200% of control levels. In contrast, AT1A mRNA expression in kidneys of 4-copy mice was only 133% of wild-type. This suggests that transcriptional regulation of the \textit{Agtr1a} gene is
complex and varies significantly between tissues. In view of
our previous studies in mice showing that duplication of the
angiotensinogen (Agt) locus causes elevations in blood pres-
sure,7 we anticipated that increasing expression of the AT1A
receptor, the major murine AT1 receptor isoform, would
likewise increase blood pressure. However, the magnitude of
the blood pressure effect of the Agtr1a gene duplication was
relatively modest, and blood pressure elevation could only be
detected in female mice.

This finding that gender modifies the phenotype in these
mouse lines is consistent with previously described gender
differences in the incidence and character of hypertension.18–20 For example, the incidence of hypertension is lower in
premenopausal women than age-matched men.21 In several
animal models of hypertension, blood pressure elevation
develops sooner and is more severe in male than female
animals.22,23 Likewise, the impact of genetic variation in the
renin-angiotensin system is also modified by gender. For
example, in several human populations, the M235T poly-
morphism in the AGT gene is associated with hypertension
and elevated circulating levels of angiotensinogen. Linkage
of the 235T allele with high blood pressure was seen in male
but not in female subjects.5 Similarly, increasing angioten-
sinogen levels in mice by increasing Agt gene copy caused a
highly significant increase in blood pressure in male mice.17
In individual female mice, the increase in blood pressure was
strongly correlated with their Agt expression in the liver, but
the correlation between gene copy number and blood pressure
failed to reach significance.17 Thus, at least for variants in the
angiotensinogen gene, the influence of gender on blood
pressure is very similar in humans and mice. In the present
study, we found clear evidence of sexual dimorphism in our
mutant animals with increased AT1A receptor expression.
However, unlike variants of the angiotensinogen gene, the
effect on blood pressure of increasing expression of AT1A
receptors was only seen in female mice. This sexual dimor-
phism is not due to differences in the levels of AT1A mRNA
expression per se. Thus, although gender effects on RAS
gene functions are pervasive, these influences are complex
and may vary dramatically between different RAS genes.

A major objective of our study was to model the capacity
for increased AT1-receptor expression to affect blood pres-
sure. Polymorphisms of the human AT1 receptor gene
(AGTR1) have been identified and one variant, A1166C, has
been associated with hypertension,24 changes in aortic disten-
sibility,25 and increased left ventricular mass.26 Careful
hemodynamic studies in nonhypertensive individuals have sug-
gested that this polymorphism may affect baseline renal
function and physiological responses to angiotensin II.27 The
A1166C nucleotide substitution is located outside the coding
region within the 3′ untranslated region of the AT1 receptor
mRNA, and it is not clear how this substitution could affect
AT1 receptor expression or function, unless it alters mRNA
stability or is in linkage disequilibrium with other mutations
in the AGTR1 gene. To date, no alterations in levels of AT1
receptor expression have yet been documented between
individuals with the different AGTR1 alleles, with the caveat
that changes in AT1 receptor expression would be difficult to
measure in humans because of the relative inaccessibility of
structures with high levels of expression such as glomeruli.
Nonetheless, our studies would predict that the consequences
of any mutations that modestly increase AT1 receptor expres-
sion will be affected by gender.

It is noteworthy that the magnitude of the impact of
alterations of AT1A receptor expression on blood pressure
changes varies markedly, depending on whether expression is
increased or decreased. We previously demonstrated that
incremental reductions in AT1A receptor levels caused rela-
tively large reductions in blood pressure that were propor-
tional to the gene copy number.8 By contrast, in the current
study, increasing AT1A receptor levels up to 2-fold had only a
modest effect on blood pressure that was gender-dependent.
These findings suggest that the capacity to compensate for
reduced expression of AT1 receptors is limited, whereas the
capacity to compensate for enhanced AT1 receptor levels is
more robust, perhaps because of the pathological conse-
quences of increasing AT1 receptor activity.

Two previous studies found that transgenic mice with
enhanced expression of AT1 receptors in cardiac myocytes
have massive cardiac enlargement, congestive heart failure,
and early death.28,29 This is in obvious contrast to the
relatively benign phenotype of our animals with enhanced
AT1-receptor expression from duplication of the Agtr1a
locus. However, there are fundamental differences in the
studies that probably explain the different phenotypes. In our
experiments, the increase in expression of the AT1 receptors
was modest and was under the control of the natural regula-
tory elements present in the Agtr1a gene. By contrast, the
cardiac-specific expression of AT1 receptors was generated in
the transgenics by using the heterologous α-MHC promoter,
and the level of expression was very high. It is likely that
aberrant levels, pattern, and dynamics of AT1 expression are
responsible for their dramatic phenotype. Differences in the
genetic backgrounds of the mice may also account for the
different outcomes of these experiments.

Along with its effects on blood pressure, duplication of the
Agtr1a gene significantly affected expression of other genes
that regulate cardiovascular functions. As with blood pres-
sure, the effects on gene expression differed between male
and female mice. In female mice, increasing Agtr1a gene
copies caused a series of apparently interrelated changes in
gene expression that probably affected blood pressure regu-
lation. Previous studies have demonstrated that AT1-receptor
activation in adrenal glomerulosa cells stimulates expression
of aldosterone synthase.30,31 Accordingly, increasing the
number of AT1A receptors in female mice was sufficient to
enhance expression of aldosterone synthase mRNA, and this
may have contributed directly to blood pressure elevation.
In contrast, expression of aldosterone synthase was not affected
in male mice with increased Agtr1a gene copies, paralleling
the lack of a blood pressure effect. In the female 3-and 4-copy
mice, the elevation in blood pressure may have triggered a
compensatory inhibition of renin mRNA expression, attenu-
ating the degree of blood pressure increase. Kallikrein
expression was also enhanced in the female mice, and this
change may also blunt the rise in blood pressure. In the male
mice, there were no alterations in renin and kallikrein
expression, indicating that increased blood pressure may have
been the trigger for these compensatory responses. Because the level of blood pressure seen in the 3- and 4-copy female mice was not different from wild-type males, the blood pressure threshold required to affect these gene expression programs may differ between male and female mice. The gender-related differences in gene expression observed in the present study and our previous study are consistent with conserved patterns of response to genetic variants within the RAS.

We also found evidence for vascular compensations that would tend to countermand the effects of the Agtr1a gene duplication on blood pressure. In the 4-copy mice, vasoconstrictor responses after infusion of relatively low concentrations of angiotensin II were blunted substantially, but at higher concentrations, the effects of these compensations were overcome. Thus, there appear to be natural mechanisms that oppose or ameliorate the potentially maladaptive consequences of exaggerated AT1 receptor expression in vasculature. These compensatory mechanisms were overcome by high-dose angiotensin II. The nature of these inhibitory mechanisms is not clear. Since AT1-specific binding is negatively modulated by angiotensin II receptor homodimers or heterodimers with other GPCRs or in receptor-receptor interactions. The formation of these heterodimers may occur through changes in the stoichiometrics of receptor interactions with downstream signaling molecules such as G proteins or in receptor-receptor interactions. The formation of AT1-receptor homodimers or heterodimers with other GPCRs may modulate activation and receptor signaling. Further understanding and characterization of these pathways that negatively modulate AT1-receptor signaling will have obvious applications to therapeutics and to understanding disease pathogenesis.

Perspectives

We have generated a mouse model for testing the capacity of genetic variants that increase expression of AT1 receptors to cause hypertension. Our studies suggest that the impact of increased Agtr1a gene expression on blood pressure will be modified by gender, by vascular compensations, and by altered expression of other genes involved in cardiovascular regulation. Thus, even for a key component of the renin-angiotensin system, the potential for incremental changes in expression of a single gene to affect blood pressure is buffered by compensations at a number of levels. Moreover, these compensations are also subject to genetic regulation that may vary between male and female subjects. Accordingly, more profound changes in blood pressure may be expected when there are concomitant mutations in genes within compensatory pathways. This is consistent with current views suggesting a polygenic basis for human hypertension.

Acknowledgments

This work was supported by National Institutes of Health grants GM20079, HL49277, and HL56122. We thank Edward Gilroy for advice on statistical analysis and Christopher Best and Kamie Snow for technical assistance.

References


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_Hypertension._ 2003;42:507-514; originally published online September 8, 2003;
doi: 10.1161/01.HYP.0000092000.07559.57

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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